O‘ZBEKISTON MILLIY UNIVERSITETI HUZURIDAGI
ILMIY DARAJALAR BERUVCHI
DSc.03/2025.27.12.K.01.13.M RAQAMLI ILMIY KENGASH
O‘ZBEKISTON MILLIY UNIVERSITETI

YAXSHILIKOVA ZARIFA ABDIMANNONOVNA

SITIZIN VA MORFOLINNI ALKILLASH VA ALKIL MAHSULOTLARI ASOSIDA SINTEZLAR

02.00.03 – Organik kimyo

Kimyo fanlari bo‘yicha falsafa doktori (PhD) dissertatsiyasi
AVTOREFERATI

Toshkent – 2026

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Contents of dissertation abstract of doctor of philosophy (PhD) on chemical sciences

Оглавление автореферата диссертации доктора философии (PhD) по химическим наукам

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Falsafa doktori (PhD) dissertatsiyasi mavzusi O‘zbekiston Respublikasi Oliy ta’lim, fan va innovatsiyalar vazirligi huzuridagi Oliy attestatsiya komissiyasida B2024.2PhD/K761 raqam bilan ro‘yxatga olingan.

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Ilmiy rahbar:	**Xoliqov Tursunali Suyunovich** kimyo fanlari doktori, professor
Rasmiy opponentlar:	**Maxsumov Abdulhamid G‘afurovich** kimyo fanlari doktori, professor
	Matchanov Alimjon Davletbayevich kimyo fanlari doktori, professor
Yetakchi tashkilot:	**Toshkent farmatsevtika instituti**

Dissertatsiya himoyasi O‘zbekiston Milliy universiteti huzuridagi DSc.03/2025.27.12.K.01.13.M raqamli Ilmiy kengashning 2026-yil “___” _____ soat ____ dagi majlisida bo‘lib o‘tadi (Manzil: 100174, Toshkent shahri Universitet ko‘chasi 4-uy. Tel.: (+99871) 246-07-88; faks: (+99871) 246-53-21; e-mail: www.ilmiy_kengash@nuu.uz).

Dissertatsiya bilan O‘zbekiston Milliy universitetining Axborot-resurs markazida tanishish mumkin (№___raqami bilan ro‘yxatga olingan). Manzil:100174, Toshkent shahri, Universitet ko’chasi 4-uy. Tel.: (+99871)246-07-88; (+99871)227-12-24, faks: (+99871)246-53-21; e-mail: nauka@nuu.uz).

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(2026-yil “___” _____ dagi _____ raqamli reyestr bayonnomasi).

M.A.Maxkamov
Ilmiy darajalar beruvchi
Ilmiy kengash raisi o‘rinbosari,
k.f.d., professor

U.O‘.Ro‘zmetov
Ilmiy darajalar beruvchi
Ilmiy kengash ilmiy kotibi,
k.f.d., professor

A.K.Abdushukurov
Ilmiy darajalar beruvchi
Ilmiy kengash qoshidagi
Ilmiy seminar raisi, k.f.d., professor

KIRISH (falsafa doktori (PhD) dissertatsiyasi annotatsiyasi)

Dissertatsiya mavzusining dolzarbligi. Bugungi kunda dunyoda morfolin va sitizin hosilalari tibbiyotda hamda farmatsevtikada turli kasalliklarga qarshi dori vositalari, agrosanoatda gerbitsid va fungitsid sifatida keng miqyosda qo‘llaniladi. Morfolin hosilalari antibiotik *linezolid*, antidepressant *reboxetine*, teri va tirnoq zamburug‘ kasalliklarida *amorolfine*, saratonga qarshi *gefitinib* preparatlar ko‘rinishida ishlatiladi. Sitizin asosida olingan *tabeks* preparati chekishga qarshi vosita sifatida qo‘llaniladi. Bu preparatlarning analoglarini yaratish, ularni olish usullarini takomillashtirish va amaliyotga qo‘llash muhim amaliy ahamiyat kasb etadi.

Jahonda morfolin va sitizinning N-alkil birikmalarini sintez qilishning samarali usullarini ishlab chiqish hamda ushbu reaksiyalar uchun yangi katalizatorlarni tavsiya etish yo‘nalishida keng ko‘lamli tadqiqotlar olib borilmoqda. Jumladan, morfolinning alkil, allil, propargil galogenidlar va sitizinning dibromalkanlar bilan alkillash reaksiyalari asosida olingan N-alkil, N-allil,
N-propargilmorfolinlarni benzil xlorid ishtirokida alkillash natijasida to‘rtlamchi ammoniy birikmalarini sintez qilish reaksiyalari muhim ilmiy ahamiyatga ega.

Respublikamizda so‘nggi yillarda ilmiy tadqiqot mavjud bilimlarni oshirishga qaratilgan va tadqiqotni sanoatlashtirish, sanoatni rivojlantirishning uzviy bog‘liqligini ta’minlash, mahalliy xomashyo asosida import o‘rnini bosuvchi mahsulotlar ishlab chiqarish borasida tabiiy va sintetik organik moddalar olish bo‘yicha muhim natijalarga erishilmoqda. 2022-2026-yillarga mo‘ljallangan Yangi O‘zbekistonning taraqqiyot strategiyasida “Milliy iqtisodiyot barqarorligini ta’minlash va yalpi ichki mahsulotda sanoat ulushini oshirishga qaratilgan sanoat siyosatini davom ettirib, sanoat mahsulotlarini ishlab chiqarish hajmini 1,4 barobarga oshirish”ga yo‘naltirilgan vazifalari belgilab berilgan[1]. Shu yo‘nalishda, bugungi kunda tarkibida azot atomi tutgan geterohalqali birikmalarni alkillash reaksiyalari asosida to‘rtlamchi ammoniy birikmalari sintezining optimal sharoitlarini topish va olingan birikmalarning tuzilishini zamonaviy fizik-kimyoviy usullar bilan tahlil qilish, reaksiyaning yuqori unumlar bilan borishiga ta’sir etuvchi asosiy omillarni va reaksiya qonuniyatlarini aniqlash, olingan birikmalarning fizik-kimyoviy va biologik xossalarni aniqlash hamda tarkibida turli funksional guruh tutgan biologik faol moddalarni yaratish uchun zarur bo‘lgan ilmiy tadqiqot ishlarini kengaytirish muhim hisoblanadi.

O‘zbekiston Respublikasi Prezidentining 2018-yil 25-oktyabrdagi PQ-3983-son “O‘zbekiston Respublikasida kimyo sanoatini jadal rivojlantirish chora-tadbirlari to‘g‘risida” qarori, 2019-yil 3-apreldagi PQ-4265-son “Kimyo sanoatini yana-da isloh qilish va investitsion jozibadorligini oshirish to‘g‘risida”gi qarori hamda 2020-yil 12-avgustdagi PQ-4805-son “Kimyo va

[1] O‘zbekiston Respublikasi Prezidentining 2022-yil 6-iyuldagi PF-60-sonli “2022-2026-yillarga mo‘ljallangan yangi O‘zbekistonning taraqqiyot strategiyasi to‘g‘risida”gi Farmoni.

biologiya yo‘nalishlarida uzluksiz ta’lim sifatini va ilm-fan natijadorligini oshirish chora-tadbirlari to‘g‘risida”gi qarorlari hamda mazkur faoliyatga tegishli boshqa me’yoriy-huquqiy
hujjatlarda belgilangan vazifalarni bajarishga muayyan darajada xizmat qiladi.

Tadqiqotning respublika fan va texnologiyalari rivojlanishining ustuvor yo‘nalishlariga mosligi. Mazkur tadqiqot respublika fan va texnologiyalar rivojlanishining VII. “Kimyo fanlari, kimyoviy texnologiyalar va nanotexnologiyalar” ustuvor yo‘nalishlarga muvofiq bajarilgan.

Muammoning o‘rganilganlik darajasi. Dunyoning ko‘pgina rivojlangan mamlakatlarida geterohalqali birikmalarni alkillash reaksiyalari organik kimyo yo‘nalishida keng o‘rganilgan, xususan, xorijda maqsadli sintezlarni amalga oshirish bo‘yicha jahonning yetakchi olimlari ilmiy tadqiqot ishlarini olib bormoqda. A.Coe, J.L.Stolerman, R.A.Clarke sitizinning nikotin retseptorlariga ta’siri va strukturaviy analoglarini o‘rganish bo‘yicha fundamental ishlar olib borgan. I.D.M.Toth, J.R.Livingstone sitizin va uning N-alkillangan hosilalarining tuzilish-faollik bog‘liqligini o‘rganishgan. H.R.Snyder, R.Adams azot saqlovchi geterotsikllar, jumladan morfolinning alkillanish reaksiyalarini klassik organik kimyo nuqtayi nazaridan o‘rganishgan. Yevropa farmatsevtik kimyo maktablari morfolin asosidagi N-alkillangan hosilalar va to‘rtlamchi ammoniy tuzlarini sintez qilish hamda ularning biologik faolligini baholash bilan shug‘ullangan

Respublikamizda morfolin va sitizin birikmalari asosida to‘rtlamchi ammoniy birikmalar sintezi hamda alkil, allil, propargilgalogenidlar bilan alkillsh reaksiyalari ustida bir qancha etakchi olimlar ilmiy izlanishlar olib borganlar, masalan S.Yu.Yunusov va hamkasblari, Sh.B.Raximov, V.I.Vinogradova, A.G‘.Maxsumov, H.S.Tojimuhamedov, O.Sh.Xoliqova, O.S.Maksumova va boshqalar o‘simliklardan sitizin ajratib ajratib olib, uning birikmalari hamda morfolin hosilalari sintezi va kimyoviy xossalari bo‘yicha ilmiy tadqiqotlar olib borganlar.

Adabiyotlar tahlilining ko‘rsatishicha, morfolin va sitizin birikmalarining
N-alkil mahsulotlar sintezi bo‘yicha keng qamrovli tajriba natijalari bo‘lishiga qaramasdan, ularning N-allil (propargil)-N-benzil, N-alkil-N-benzil, ba’zi bir
N-alkil sitizinlar o‘rganilmagan. Shu sababli, alkil galogenidlar va digalogenalkanlar bilan reaksiyalarini o‘rganish va sintez qilingan birikmalarning biologik faolligini aniqlash alohida ilmiy qiziqish kasb etadi. Shu sababli mazkur dissertatsiya ishi morfolinni alkillash natijasida olingan N-alkilmormolinlarni benzil xlorid bilan nukleofil almashinish reaksiyalarini tadqiq qilish hamda sitizinni dibromalkanlar ishtirokida biologik faol hosilalarini maqsadli sintezini amalga oshirishga qaratilgan.

Tadqiqotning dissertatsiya bajarilgan ilmiy-tadqiqot muassasasining ilmiy tadqiqot ishlari bilan bog‘liqligi. Dissertatsiya O‘zbekiston Milliy

universitetining AM-FZ-2019081452 “Etilen asosida siklogeksan sintezi texnologiyasini ishlab chiqish” (2020-2022-yy.) mavzularidagi fundamental ilmiy tadqiqodlar doirasida bajarilgan.

Tadqiqotning maqsadi Sitizin va morfolinni alkillash va alkil mahsulotlari asosida sintezlarni amalga oshirishdan iborat.

Tadqiqotning vazifalari: Morfolinni turli alkillovchi reagentlar (monoalkilgalogenidlar) bilan o‘zaro ta’sirlanish reaksiyalarini hamda alkillash reaksiyalarining alkillovchi agent tabiatiga bog‘liqligini aniqlash;

Sintez qilingan N-pentil-, N-nonil-, N-allil- va N-propargilmorfolinlarning benzil xlorid bilan nukleofil almashinish reaksiyalarini olib borish;

Sitizinning turli dibromalkanlar bilan reaksiyalarida kechadigan N-alkillanish va ichki halqalanish jarayonlarini asoslash;

Sintez qilingan yangi birikmalarning tuzilishini zamonaviy fizik-kimyoviy usullar (IQ, ^{1}H va ^{13}C YaMR, hamda rentgen-tuzilish tahlil) yordamida tasdiqlash;

Olingan sitizin hosilalari va morfolin asosida olingan to‘rtlamchi ammoniy tuzlarining biologik faolligini (in vitro sharoitida gram-musbat/manfiy bakteriyalar va zamburug‘larga nisbatan) aniqlash.

Tadqiqotning obyektlari sifatida sitizin va morfolin**,** alkillovchi reagentlar, alkil hosilalari, to‘rtlamchi ammoniy tuzlari tanlangan.

Tadqiqotning predmeti sitizin va morfolinning alkillanish reaksiyalari, ushbu kimyoviy jarayonlarning borish mexanizmlari (S_N2 va ichki halqalanish), reaksiya sharoitlariga bog‘liq holda hosil bo‘ladigan alkil hosilalar va to‘rtlamchi ammoniy tuzlarining fazoviy tuzilishi, hosil bo‘lish qonuniyatlari hamda ularning
fizik-kimyoviy xossalarini o‘rganishni o‘z ichiga oladi.

Tadqiqotning usullari sifatida yupqa qatlamli xromatografiya (YuQX), IQ, 1H va 13C YaMR-spektroskopiya, rentgen tuzilish tahlili (RTT), biologik faolliklarni aniqlash usullari.

Tadqiqotning ilmiy yangiligi.

Morfolinning monogalogenalkanlar ishtirokidagi reaksiyalarida N-butilmorfolin< N-pentilmorfolin < N-geksilmorfolin< N-nonilmorfolin qatorida CH_2-metilen guruhlar soni uzayishi bilan mahsulot unumi ortishiga asoslangan. Reaksiyalarining S_N2 mexanizmda etanol erituvchisida (78 ^{o}C) unum yuqori bo‘lishi erituvchi tabiati va reaksion haroratning mahsulot unumiga ta’siri bilan izohlangan;

Ilk bor N-alkil, (N-allil, N-propargil)morfolinlarning asetonitril erituvchisida, 4-Benzil-4-Pentil-, 4-Benzil-4-Nonil, 4-Benzil-4-Allil- hamda 4-Benzil-4-Propargilmorfoliniy xlorid kabi to‘rtlamchi ammoniy tuzlari sintez qilingan. N-allil, N-propargilmorfolinlar bilan benzilxlorid nisbati 1:1,2 bo‘lganda reaksiya unumi yuqoriligi (96 %) isbotlangan;

Sitizinni alkillash jarayonida ichki halqalangan birikma, N-(1,4-butilen) to‘rtlamchi sitizin bromidi bir bosqichda sintez qilinib, 95 % unum bilan barqaror halqali tuzilishdagi ortorombik kristall $\alpha = \beta = \gamma = 90°$ li

birikma hosil bo‘lishi tadqiq qilingan;

N-geksilmorfolin asosida temir (III) xlorid katalizatori ishtirokida 4-Geksil-4-Nonilmorfoliniy bromid sintez qilinib, Lyus kislotasining ushbu reaksiyada katalizatorlik xususiyatini namoyon etishi mumkinligi ko‘rsatilgan;

N-alkil, N-allil, N-propargilmorfolinlar IQ spektrlarida morfolinga xos N–H 3300-3400 cm^{-1} sohada tebranishlari yo‘qligi hamda 2850-2960 cm^{-1} sohada alifatik C–H yutilish chiziqlarining kuzatilishi ularning uchlamchi aminlar ekanligini tasdiqlagan. ^{1}H YaMR spektrlarida 2,20-2,35 m.u. sohalarda azot atomi bilan bog‘langan metilen guruh (H-7) signallari aniqlandi. 4-Benzil-4-nonilmorfoliniy xloridning kristall tuzilishi rentgenostruktur tahlil yordamida aniqlanib, uning monoklinik kristall sistemasida (a = 8,7990(5) Å, b = 7,4720(4) Å, c = 32,998(2) Å, β = 95,561(3)°) kristallanishi tasdiqlangan.

Tadqiqotning amaliy natijalari quyidagilardan iborat:

Morfolin asosida olingan uchlamchi aminlarning benzil xlorid bilan reaksiyalarini turli erituvchilarda olib borish va tegishli to‘rtlamchi ammoniy tuzlarini yuqori unumlarda olish mumkinligi ko‘rsatilgan. Sintez qilingan to‘rtlamchi ammoniy tuzlaridan 4-benzil-4-pentilmorfolin-4-iy va 4-benzil-4-nonilmorfolin-4-iylarning hamda sitizinning 1,4-dibrombutan bilan hosil qilgan birikmasining fazoviy tuzilishi hamda barcha kristallografik kattaliklari isbotlangan va xalqaro Kembridj kristallografik ma’lumotlar bazasi (Cambridge Crystallographic Data Centre)ga shunga o‘xshash birikmani sintez qilishda foydalanish uchun joylashtirilgan;

Sintez qilingan moddalardan 4-Benzil-4-Nonilmorfoliniy xlorid, va N-(5-brompentil) sitizinning *Bacillus subtilis, Staphylococcus aureus* grammusbat, *Escherichia coli, Pseudomonas aeruginosa* grammanfiy bakteriyalarga qarshi bakterisidlik, shuningdek 4-Benzil-4-Allilmorfoliniy xlorid *Candida albicans* patogen zamburug‘larga qarshi fungisidlik faolliklarini namoyon qilishi aniqlangan.

Tadqiqot natijalarining ishonchliligi. Tadqiqot natijalari spektral usullar (YMR, IQ,), rentgen tuzilish tahlili (RTT), xromatografik (YQX) va biologik usullar ma’lumotlari asosida tasdiqlangan, shuningdek, tadqiqot natijalarining ishonchliligi xalqaro ilmiy jurnallarda chop etilganligi bilan izohlanadi.

Tadqiqot natijalarining ilmiy va amaliy ahamiyati. Tadqiqot natijalarining ilmiy ahamiyati shundan iboratki, sitizin alkaloidi va morfolinni alkillash,

N-alkilmahsulot asosida ilk bora to‘rtlamchi ammoniy tuzlarini hamda sitizin asosida bir bosqichda ichki halqalangan mahsulot sintez qilinganligi, shuningdek, tarkibi, tuzilishi, xossalari va barqarorligini aniqlash natijalari hamda xulosalarni zamonaviy fizik-kimyoviy tahlil usullari natijalariga tayangan holda amalga oshirilganligi geterotsiklik birikmalar kimyosini nazariy jihatdan yangi materiallarga boyitganligi bilan izohlanadi.

Tadqiqot natijalarining amaliy ahamiyati shundan iboratki, sintez

qilingan to‘rtlamchi ammoniy tuzlaridan 4-benzil-4-pentilmorfolin-4-iy va 4-benzil-4-nonilmorfolin-4-iylarning hamda sitizinning 1,4-dibrombutan bilan hosil qilgan birikmasining mono kristallari o‘stirilib, fazoviy tuzilishi hamda barcha kristallografik kattaliklari isbotlangan va xalqaro Kembridj kristallografik ma’lumotlar bazasi (Cambridge Crystallographic Data Centre)ga kiritildi. 4-Benzil-4-Nonilmorfoliniy xlorid, 4-Benzil-4-Allilmorfoliniy xlorid va N-(5-brompentil)sitizinning ma’lum konsentratsiyalarda bakteriya hamda zamburug‘larga nisbatan sezilarli antibakterial va antifungal faollik namoyon qiluvchi alkil hosilalar aniqlangan. Sitizin va morfolin asosida biologik faol moddalar olindi hamda turli alkillovchi reagentlar ta’sirida qator yangi birikmalarni samarali olish imkoniyati yaratilishi bilan asoslanadi.

Tadqiqot natijalarining joriy qilinishi. N-pentil morfolin, N-nonil morfolin va sitizin asosida olingan yangi to‘rtlamchi ammoniy tuzlari sintezi, kimyoviy modifikatsiyasi bo‘yicha olingan ilmiy natijalar asosida: uchta birikmaning kristall tuzilishlari aniqlangan va xalqaro Markaziy Kembridj kristallografik ma’lumotlar bazasiga kiritilgan bo‘lib (The Cambridge Structural Database, https://www.ccdc.cam.ac.uk) CCDC: 2277070, 2541862, 2541863 ularga tegishli identifikatsiya raqamlari olingan. Natijada o‘xshash birikmalarni sintez qilish va fazoviy tuzilishlarini taqqoslab o‘rganish imkonini bergan.

Olingan natijalar O‘zbekiston Milliy universitetida bajarilgan FL–7923051904 “Vinil birikmalar olish uchun nano o‘lchamli katalizatorlar va ularning tashuvchilari sintezi, tuzilishi va elektron xossalari” (2024-2025-yy.) mavzusida bajarilgan fundamental loyihada foydalanilgan (O‘zbekiston Respublikasi Oliy ta’lim, fan
va innovatsiyalar vazirligi huzuridagi Innovatsion rivojlanish agentligi 2026-yil 22-aprel 01-02/1/1677-son ma’lumotnomasi). Natijada yangi birikmalarni sintez qilish, ularning kristall tuzilishi va fizik-kimyoviy xossalarini aniqlash bo‘yicha uslubiy yondashuvlar boyitildi, olingan ilmiy natijalar esa istiqbolli funksional materiallarni yaratish va ularning xossalarini baholashga oid tadqiqotlarda qo‘llashga erishilgan.

Tadqiqot natijalarining aprobatsiyasi. Mazkur tadqiqot natijalari 7 ta, jumladan 2 ta xalqaro va 5 ta respublika ilmiy-amaliy anjumanlarida ma’ruza qilingan hamda muhokamadan o‘tkazilgan.

Tadqiqot natijalarining e’lon qilinganligi. Dissertatsiya mavzusi bo‘yicha jami 11 ta ilmiy ish chop etilgan, O‘zbekiston Respublikasi Oliy attestatsiya komissiyasining falsafa doktori (PhD) dissertatsiyalari asosiy ilmiy natijalarini chop etish tavsiya etilgan ilmiy nashrlarda 4 ta maqola, jumladan, 1 xorijiy (scopus), 3 ta respublika jurnallarida nashr etilgan.

Dissertatsiya tuzilishi va hajmi. Dissertatsiya tarkibi kirish, uchta bob, xulosa, foydalangan adabiyotlar ro‘yxati va ilovalardan iborat. Dissertatsiyaning hajmi 110 betni tashkil etadi[2].

DISSERTATSIYANING ASOSIY MAZMUNI

Kirish qismida o‘tkazilgan tadqiqotlarning dolzarbligi va zarurati haqida ma’lumot berilgan, maqsad va vazifalari keltirib o‘tilgan, obyekti va predmeti tavsiflangan, tadqiqotning respublika fan va texnologiyasi rivojlanishining ustuvor yo‘nalishlariga mos kelishi ko‘rsatilgan, tadqiqot natijalarining ilmiy yangiligi va amaliy ahamiyati bayon etilgan, olingan natijalarning ilmiy va amaliy ahamiyati, ularning amaliyotga tatbiq qilinishi ochib berilgan, shuningdek, chop etilgan ishlar hamda dissertatsiya tuzilishi bo‘yicha ma’lumotlar keltirilgan.

Dissertatsiyaning **“Morfolin va sitizin asosida to’rtlamchi ammoniy tuzlari sintezi”** deb nomlangan **birinchi bobida** adabiyotlar tahlili keltirilgan bo‘lib, morfolin asosida sintezlar, sitizin asosida sintezlar va to‘rtlamchi ammoniy tuzlarining olinishi hamda ularning xossalari to‘g‘risidagi ma’lumotlar tahlil qilingan. Ularning sintezi, modifikatsiyasi, biologik faolligiga doir adabiyotlarning hozirgi holati tahlil qilingan. Dissertatsiyaning “**N-alkilmorfolinlar sintezi va ular asosida**

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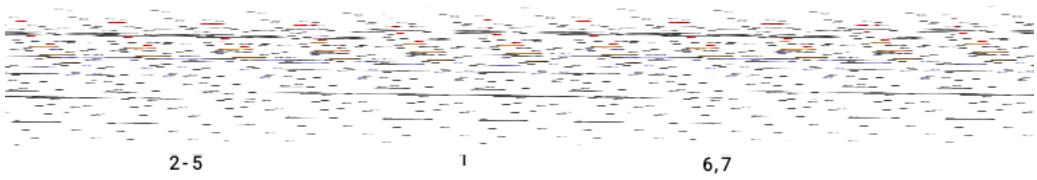
[2]*Muallif O‘zR FA O‘simlik moddalari kimyosi instituti yetakchi ilmiy xodimi Sh.N. Jo‘raqulovga dissertatsiya ishini bajarishda ko‘rsatgan yordami uchun o‘zining samimiy minnatdorchiligini bildiradi.*

to‘rtlamchi ammoniy tuzlarini olish hamda Sitizinni dibromalkanlar bilan turli hosilalari sintezi” deb nomlangan **ikkinchi bobida** tadqiqot natijalari keltirilgan.

Morfolinning butil, pentil, geksil va nonil bromidlar bilan olib borilgan reaksiyalari, jarayonning optimal sharoitlarini (erituvchi turi, harorat, reagentlar nisbatlari va reaksiya davomiyligi) tanlash bo‘yicha o‘tkazilgan tadqiqotlar natijalari batafsil bayon etilgan. Shu bilan birga, alkil zanjir uzunligining reaksion qobiliyatga, hosil bo‘ladigan mahsulotlarning unumi qiyosiy tahlil qilinib, eng samarali sharoitlar aniqlangan. Morfolin bilan alkilgalogenidlarning reaksiyasini amalga oshirish uchun reaksiya mahsulotining unumiga erituvchilar, vaqt va modda tabiati kabi omillar ta’siri o‘rganildi. Erituvchilar sifatida etanol va atsetondan foydalanildi. Natijalarni quyida ko‘rishimiz mumkin.



1-sxema. Morfolinning to‘yingan va to‘yinmagan alkilbromidlar bilan reaksiyalari.

1-jadval

Morfolinni alkil galogenidlar bilan reaksiyalari unumiga vaqt va erituvchining ta’siri. (Morfolin : alkilgalogenid: K_2CO_3, 1:1:1)

№	Reagentlar	Mahsulot unumi % va reaksiya davomiyligi (soat)

	1:1:1	1 soat		3 soat		4 soat		5 soat		7 soat	
		aseton	etanol	aseton	etanol	aseton	etanol	aseton	etanol	aseton	etanol
2	Morfolin:Butilbromid: K_2CO_3	50	52	50	55	60	68	60	68	-	-
3	Morfolin: Pentilbromid:K_2CO_3	66	75	70	81	70	81	-	-	-	-
4	Morfolin: Geksilbromid: K_2CO_3	43	52	59	68	74	82	74	82	-	-
5	Morfolin: Nonilbromid:K_2CO_3	42	51	53	62	65	70	67	74	78	86

Uglerod zanjirining uzayishi mahsulot unumiga bir nechta termodinamik va kinetik omillar orqali ijobiy ta’sir ko‘rsatadi. Birinchidan, alkil zanjiri uzunligi ortgan sari (butilbromiddan nonilbromidgacha) alkilgalogenidning qaynash harorati sezilarli darajada oshib boradi va uning uchuvchanligi kamayadi. Reaksiya 5-7 soat davomida teskari sovutgich ostida qaynatilganligi sababli, nisbatan qisqa zanjirli reagentlarning (masalan, butilbromid) ma’lum qismi bug‘lanish hisobiga reaksiya muhitidan uzoqlashishi mumkin. Nonilbromid kabi og‘irroq reagentlarda bu yo‘qotish deyarli kuzatilmaydi va effektiv konsentratsiya yuqori darajada saqlanib qoladi.

Ikkinchidan, uzun zanjirli (tarmoqlanmagan) birlamchi alkilgalogenidlarda nonilbromidning lipofilligi yuqori bo‘lishi uning organik fazadagi oraliq komplekslar barqarorligiga hissa qo‘shishi va reaksiyaning yakuniy unumdorligini 86 %gacha oshirishi ilmiy tasdig‘ini topdi.

Nazariy jihatdan, bunday reaksiyalar uchun aproton qutbli erituvchilar (masalan, aseton) eng maqbul hisoblanadi, chunki ular nukleofilni solvatlamaydi va uning reaksiyaga kirishish qobiliyatini oshiradi. Shu sababli, klassik qarashlarga ko‘ra, atseton muhitida reaksiya tezligi va mahsulot unumi yuqori bo‘lishi kutiladi.

Biroq mazkur tadqiqotdagi amaliy natijalarning etanol erituvchisida unum yuqori bo‘lishi termodinamik harorat omili va erituvchilarning fizik xossalari bilan tushuntiriladi. Atsetonning qaynash harorati nisbatan past (56^oC), etanolniki esa yuqori (78^oC). Reaksiyalar teskari sovutgichda qaynash haroratigacha qizdirilib olib borilgan. Etanoldagi muhitda reaksiya 78^oC da boradi, bu esa reaksiyaga kirishuvchi moddalarga ko‘proq issiqlik (kinetik) energiyasi berib, S_N2 jarayonining aktivlanish energiyasi (Ea) to‘sig‘idan oshib o‘tish ehtimolini keskin oshiradi. Natijada, haroratning yuqoriligi aproton muhit beradigan afzallikni bosib ketadi va ma’lum vaqt oraliqlarida (5 soat) etanol muhitida mahsulot unumi sezilarli darajada yuqoriroq bo‘lishini ta’minlaydi.

Shu bois, etanol erituvchisida mahsulot unumining asetonga nisbatan yuqori bo‘lishi fizik-kimyoviy omillar yig‘indisi bilan izohlanadi va tajribaviy natijalar bilan mos keladi.

2-jadval

Morfolin bilan alkilgalogenidlarning reaksiyasidan olingan mahsulotlarning unumi va fizik-kimyoviy kattaliklari

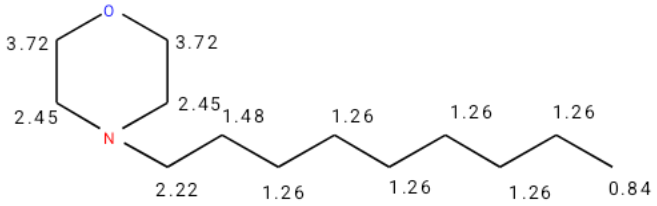
№	Olingan mahsulot	Reagentlar mol nisbati	Vaqt, soat	Rf qiymati	Mahsulot unumi, %	$T_{qaynash}$, C^o	Agregat holati,rangi
2	N-butilmorfolin	1:1	4	0,71	68	178–182	Suyuq, och sariq
3	N-pentilmorfolin	1:1	3	0,77	81	195–200	Suyuq, och sariq
4	N-geksilmorfolin	1:1	5	0,69	82	215–220	Suyuq, och sariq
5	N-nonilmorfolin	1:1	7	0,66	86	270–280	Yog‘simon suyuqlik, sarg‘ish

Ushbu ishda morfolinning alkilgalogenidlar bilan 1:1 mol nisbatda olib borilgan alkillash reaksiyalari asosida N-alkilmorfolinlar qatori sintez qilindi. Tadqiqotda N-butil-, N-pentil-, N-geksil- va N-nonilmorfolinlar olinib, ularning reaksiya kinetikasi, unum ko‘rsatkichlari hamda fizik-kimyoviy xossalari o‘rganildi.

Alkil zanjir uzaygani sari sterik to‘siq ortadi, shuningdek, reagentlarning fazoviy xossalari (viskozlik va diffuziya tezligi) pasayadi, bu esa reaksiya tezligini kamaytiradi. Ayniqsa, C_6 va C_9 atomli alkilgalogenidlar ishtirokidagi reaksiyalarda diffuzion cheklanishlar muhim rol o‘ynaydi.

YuQX tahlillari barcha sintez qilingan birikmalar uchun Rf qiymatining bir biriga yaqin ekanligini ko‘rsatdi. Bu holat ishlatilgan eluent tizimi sharoitida
N-alkilmorfolinlarning qutblilik xossalari yaqin ekanligini va asosiy farq faqat alkil zanjir uzunligida ekanligini tasdiqlaydi. Morfolin halqasining doimiy qutbli fragment sifatida saqlanishi Rf qiymatlarining sezilarli o‘zgarmasligiga sabab bo‘ladi.

Umuman olganda, olingan natijalar morfolinning alkilgalogenidlar bilan alkillash reaksiyasi 80°C sharoitda samarali kechishini, 1:1 mol nisbat optimal ekanligini hamda sintez qilingan N-alkilmorfolinlar yuqori unum bilan olinishi mumkinligini ko‘rsatdi. Kuzatilgan kinetik va termodinamik qonuniyatlar ushbu birikmalar sinfi organik sintez hamda sirt-faol moddalar kimyosi uchun istiqbolli ekanligini tasdiqlaydi.

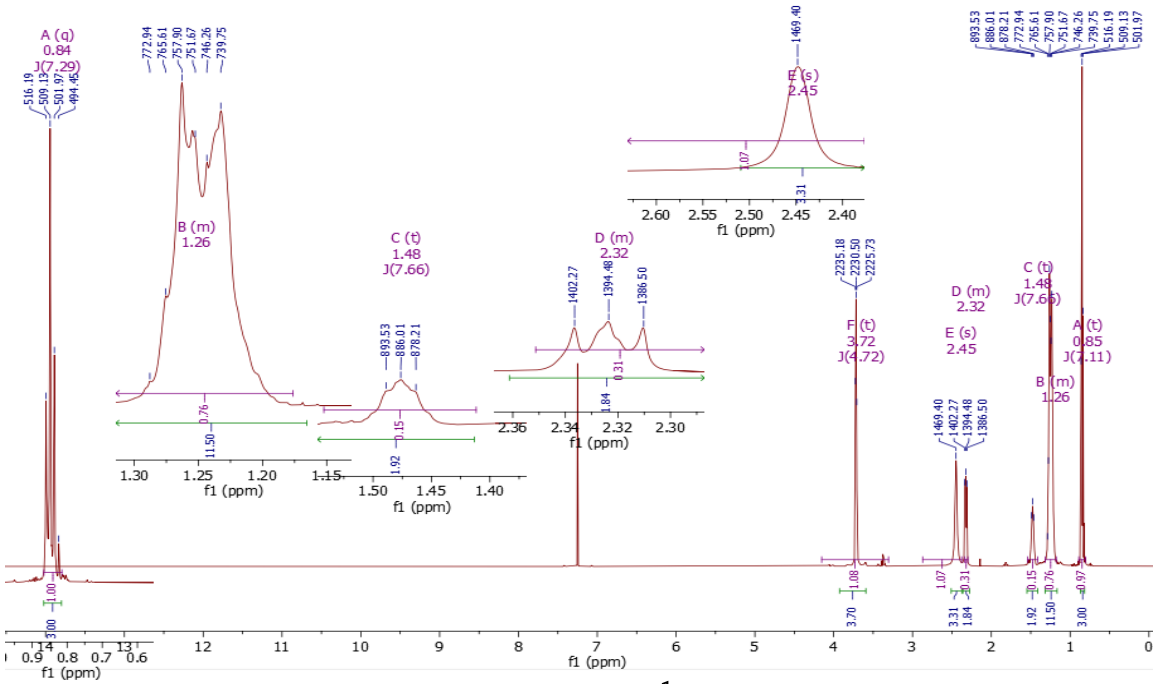


N-nonilmorfolinning (5) ^1H va ^{13}C YaMR-spektrlari tahlili.

N-nonilmorfolinning (**5**) ^1H YaMR spektrida dastlabki morfolindan

farqli ravishda 0.84 m.u. sohasida metil guruh tutgan (CH_3) H-15 protonlariga xos triplet (J= 7.1) signal aniqlandi. 1.26 m.u. sohasida metilen guruh tutgan (CH_2)
H-9,10,11,12,13,14 protonlariga xos multiplet signallar aniqlandi. 1.48 m.u. sohasida metilen guruhiga H-8 protonlarga xos triplet (J=7.7) signallarni ko‘rishimiz mumkin. 2.32 m.u. sohasida morfolin halqasidagi azot atomi bilan bog‘langan metilen guruh (CH_2) H-7 protonlariga xos multiplet signallar aniqlandi. Qolgan signallar morfolin molekulasiga xos signallar ekanligi kuzatildi.

^{13}C YaMR spektrini 14.18 m.u. sohasida nonil molekulasidagi metil guruh (C-15), 22.74 m.u. sohada 14- uglerod atomi hamda 26.43 m.u. sohada 9- uglerod atomi va 27.56 m.u. sohada 8-uglerod atomi, 29.34 m.u. sohada 12-uglerod atomi, 29.60 m.u. sohada 10-11 uglerod atomiga xos hamda, 31.94 m.u. sohada 13-uglerod atomi, 59.27 m.u. sohada morfolin halqasidagi azot atomiga bog‘langan 7-uglerod atomi signallari kuzatildi. Qolgan uglerod atomlari morfolin halqasiga xos signallar berganligini ko‘rishimiz mumkin. N-nonilmorfolinning ^{1}H va ^{13}C YaMR spektrlari tahlili sintez qilingan birikmaning tuzilishini to‘liq tasdiqladi. Spektrda nonil radikaliga tegishli proton va uglerod atomlari signallarining kuzatilishi hamda ularning kimyoviy siljish qiymatlari adabiyotlarda keltirilgan alifatik zanjirli uchlamchi aminlar uchun xarakterli diapazonlarga mos kelishi aniqlandi. Xususan, terminal metil guruhi protonlarining triplet ko‘rinishida namoyon bo‘lishi va metilen protonlarining ketma-ket multiplet signallari nonil fragmentining morfolin azot atomiga birikkanligini tasdiqlaydi. Shuningdek, morfolin halqasidagi azot atomi bilan bevosita bog‘langan metilen guruhi proton va uglerod atomlari signallarining past maydonga siljishi azot atomining elektron ta’siri bilan izohlanadi.



1-rasm. N- nonilmorfolinning **(5)** ^{1}H YaMR-spektri.

3-jadval

Morfolinni allil va propargil bromidlar bilan reaksiyalari unumiga vaqtning ta'siri. (Morfolin: alkilgalogenid: K_2CO_3, 1:1:1)

№	Reagentlar 1:1:1	Mahsulot unumi, (%) va reaksiya davomiyligi (soat)			
		1 soat	2 soat	3 soat	4 soat
6	Morfolin:Propargilbromid: K_2CO_3	63	91	92	92
7	Morfolin:Allilbromid:K_2CO_3	86	87	87	-

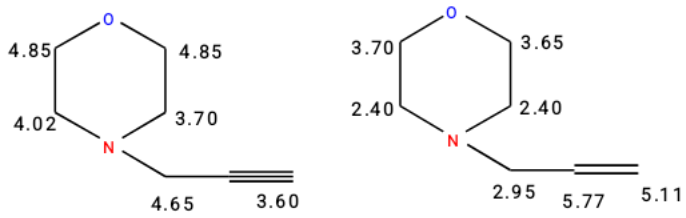
Morfolin atsetonda eritilib, so'ngra, allil va propargil bromidlar tomchilatib qo'shildi. Reaksion aralashmani magnitli aralashtirgichda 3-4 soat davomida xona haroratida aralashtirish yordamida mahsulot sintez qilindi. Morfolinning to'yinmagan allil va propargil bromidlar bilan reaksiyalari atseton kabi aproton erituvchisidan foydalanish orqali reaksiya unumi oshirildi.

4-jadval

Morfolinni allil va propargil bromidlar bilan reaksiyalari unumiga reagentlar nisbati ta'siri (Morfolin: alkilgalogenid: K_2CO_3, 1:1:1)

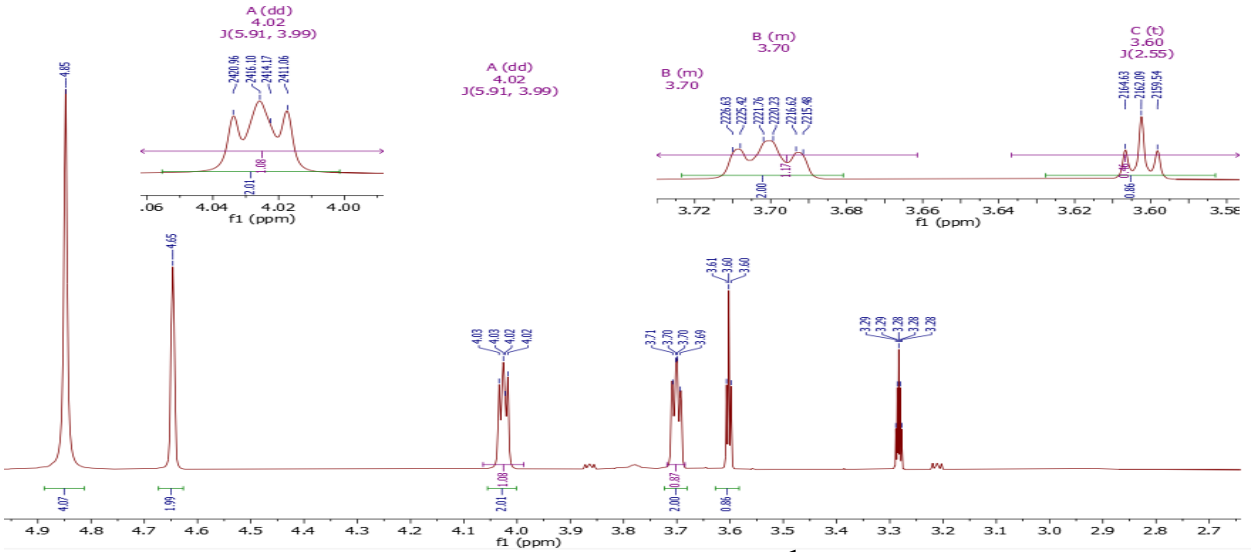
№	Reagentlar	Mahsulot unumi, (%) va reagentlar mol nisbati		
		1:1	1:1,1	1:1,2
1	Morfolin:Propargilbromid: K_2CO_3	91	92	92
2	Morfolin:Allilbromid:K_2CO_3	86	87	87

3- va 4-jadvalda Morfolinning to'yinmagan alkil bromidlar o'rtasidagi reaksiyalarga vaqt davomiyligi hamda dastlabki reagentlarning nisbati reaksiya unumiga ta'sirini o'rganish natijalari ko'rsatilgan. Reaksiya turli mol nisbatlarida 1:1, 1:1,1 va 1:1,2 hamda turli vaqt oralig'ida 1 soat, 2 soat va 3 soat (propargilbromid bilan 4 soat) davomida olib borildi. Reagentlar nisbati 1:1 bo'lganda, kam vaqt sarflanib eng yuqori unumga erishildi.



N-propargil morfolinning **(6)** ^{1}H YaMR spektrida dastlabki morfolindan farqli ravishda 3.60 m.u. sohasida molekula tarkibida uchbog' tutgan (C-H guruhi) H-9 protonlariga xos triplet signal (J= 2.6) aniqlandi. 3.70 va 4.02 m.u. sohada azot atomiga bog'langan (CH_2 guruh) H-3,5 protonlari uziga xos tarzda multiplet hamda dublet-dublet (J=5.9, 3.9) signallar, 4.65 m.u. sohada propargil molekulasidagi azot atomi bilan bog'langan (CH_2 guruhi)

H-7 protoni signalini ko‘rishimiz mumkin. 4.85 sohada kislorod atomiga bog‘langan (CH_2 guruhi) H-2,6 protonlar signali aniqlandi. Birikmaning ^{13}C YaMR spektrini 50.19 m.u. sohasida proporgil molekulasidagi azot atomi bilan bog‘langan uglerod (S-7), 69.69 m.u. sohada
9-uglerod atomi hamda 82.73 m.u. sohada 8-uglerod atomi signallari aniqlandi.

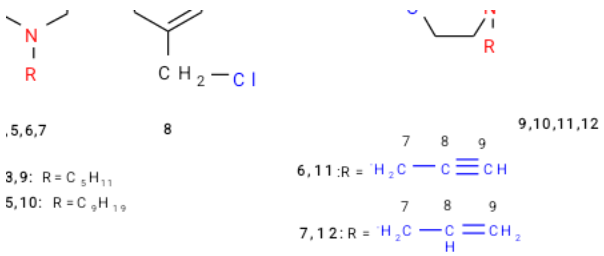


2-rasm. N-propargilmorfolinning **(6)** ^1H YaMR-spektri.

Morfolinning to‘yinmagan alkil galogenidlar bilan olib borilgan reaksiyalarida sintez mahsulotlarini tuzilishi IQ, ^1H va ^{13}C YaMR spektroskopik usulida isbotlandi.

N-Pentil, N-Nonil, N-Allil, N-Propargilmorfolinlarning benzil xlorid bilan reaksiyalari.

To‘rtlamchi ammoniy birikmalari sirt-faol, yuvuvchi va antimikrob xossalarga ega. Bu tuzlarining eng keng qo‘llanilish sohalaridan biri sanitariya va dezinfeksiya sohasi hisoblanadi. Morfolin asosida olingan to‘rtlamchi ammoniy tuzlari *Staphylococcus aureus* ATCC 25923 va *Escherichia coli* ATCC 25922 bakteriyalariga qarshi to‘liq dezinfeksiya ta’sirini namoyon etganligi aniqlangan. Bundan tashqari, tarkibida morfolin molekulasi mavjud bo‘lgan ko‘plab birikmalar biologik faol, dori vositalari hisoblanadi.



2-sxema. To‘rtlamchi ammoniy tuzlari sintezi.

Bu yerda N-pentilmorfolin (**3**), N-nonilmorfolin (**5**), N-propargilmorfolin (**6**), N-allilmorfolin (**7**), 4-Benzil-4-Pentilmorfoliniy xlorid (**9**), 4-Benzil-4-Nonilmorfoliniy xlorid (**10**), 4-Benzil-4-Propargilmorfoliniy xlorid (**11**), 4-Benzil-4-Allilmorfoliniy xlorid (**12**).

Yuqoridagi tajribalar asosida N-alkilmorfolinlar benzil xlorid bilan erituvchini qaynash haroratida qutbli apraton erituvchi atsetonitril ishtirokida ta'sirlanishidan to'rtlamchi ammoniy tuzlari yuqori unumlar bilan olindi. Olingan natijalar 5-jadvalda keltirilgan.

5-jadval

Ilk bor olingan to'rtlamchi ammoniy tuzlarining unumi va fizik-kimyoviy kattaliklari

№	Olingan mahsulotlar	Reagentlarning mol nisbati	Vaqt, soat	T_{suyuq}, °C	Rf qiymati	Mahsulot unumi, %	Agregat holati, rangi
1	4-Benzil-4-Pentilmorfoliniy xlorid	1:1,2	5,5	194-196	0,60	94	Oq, kristal
2	4-Benzil-4-Nonilmorfoliniy xlorid	1:1,2	7	196-198	0,68	89	Oq, kristal
3	4-Benzil-4-Propargilmorfoliniy xlorid	1:1,2	4,5	205-207	0,64	80	Qo'ng'ir, smolasimon
4	4-Benzil-4-Allilmorfoliniy xlorid	1:1,2	5	214-216	0,63	96	Och sariq moysimon

Morfolin asosida olinngan N-alkil morfolinlar o'z navbatida benzil xlorid bilan reaksiyalarida reagentlarning 1:1, 1:1,1, 1:1,2, 1:1,5 nisbatlarida tajribalar olib borildi, natijada 1:1,2 mol nisbatda yuqori unumga erishildi. Tajribalar turli xil vaqt davomiyligida, erituvchini qaynash haroratida olib borilganda 4-Benzil-4-Pentilmorfoliniy xlorid tuzida yuqori unum bilan mahsulot sintez qilindi. Morfolin hosilasidagi uchlamchi azot (R_3N) erkin elektron juftiga ega kuchli nukleofil bo'lib, azot benzilxloriddagi elektrofil markazga hujum qiladi.

C-Cl bog'i uziladi va C-N bog'i hosil bo'ladi. Natijada N-benzil-N-alkilmorfoliniy xlorid (to'rtlamchi ammoniy tuzlari) hosil bo'ladi. Reaksiya nukleofil almashinish (S_N2) mexanizmda boradi. Bu jarayonda reaksiya tezligiga va mahsulot unumiga alkil guruh tabiati ham bevosita ta'sir qiladi. N-pentil va N-nonil hosilalar uzun alkil zanjirga ega, buning natijasida fazoviy to'siq oshadi va reaksiya tezligi pasayadi, lekin lipofillik oshadi. N-allil hosilada π- tizim mavjud, elektrono donor effektga ega, natijada nukleofillik ortadi va reaksiya nisbatan tez boradi. N-propargil hosilada *sp*-gibridlangan uglerod mavjud, elektron tortuvchi effekt biroz kuchli bo'lib, oraliq kompleksning barqarorligi pasayishi mumkin. Bunda N-alkil hosilalarning reaksion qobiliyati quyidagi tartibda kamayib boradi:

N-allil morfolin > N-pentil morfolin ≈ N-nonil morfolin > N-propargil morfolin. Sintezda foydalanilgan atsetonitril (CH_3CN) erituvchisi qutubli

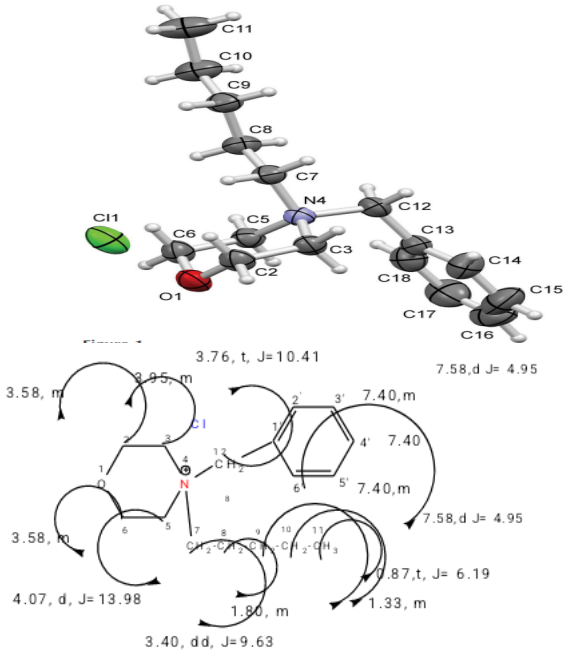
apraton erituvchi hisoblanadi. Nukleofilni solvatlamaydi, natijada S_N2 reaksiyani tezlashtiradi va to‘rtlamchi ammoniy tuzlari sintezi uchun maqbul muhit hisoblanadi. Substrat – benzilxlorid reaksion qobiliyati kuchliligi sababli reaksiyaning yuqori unum bilan borishini ta’minlaydi.

To‘rtlamchi ammoniy tuzlari antimikrob faollikga ega, fazalararo katalizatorlar sifatida ishlatiladi, bundan tashqari, dori vositalari sintezida muhim amaliy ahamiyatga ega.

Tajribalar YuQX nazorat qilib turildi (Sistema: Xloroform:Metanol: 16:1, 12:1, 4:1, 2:1). Sintez qilingan birikmalarning Rf qiymatlari aniqlangan. Sintez qilingan birikmalarning tuzilishi IQ, ^1H, ^{13}C YaMR spektroskopiya, rentgen tuzilish tahlili (3-rasm) usullari bilan tasdiqlangan.

^1H YMR (600 MHz, $CDCl_3$, δ, m.u., J/Hz): 0.87 (3H, t, J= 6.19, H-11), 1.33 (4H, m, H -9,10), 1.80 (2H, m, H-8), 3.40 (2H, dd, J= 9.63, 2.38, H-7), 3.58 (4H, m, H-2,6), 3.76 (2H, t, J=10.41 H-12), 3.95 (2H, m, H-3), 4.07 (2H, d, J=13.94 H-5), 7.40 (3H, m, H-4',3',5'), 7.58 (2H, d, J=4.95 H-2',6').

^{13}C YMR (150 MHz, $CDCl_3$, ⁄, m.u.): 13.94 (C-11), 21.84 (C-10), 22.31 (C-8), 28.42 (C-9), 56.33 (C-3,5), 56.98 (C-7), 60,62 (C-2,6), 64,85 (C-12), 126.77 (C-1’), 129.42 (C-3',5'), 130.86 (C-4'), 133.40 (C-2',6').

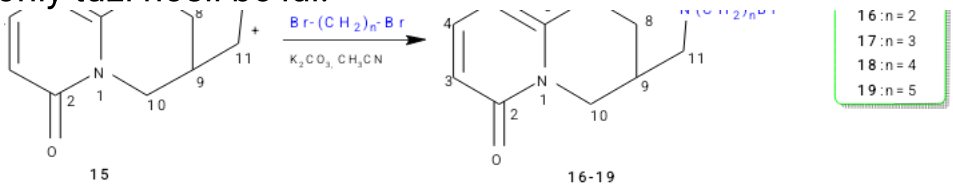


3-rasm. 9-birikmaning kristaldagi tuzilishi.

Sitizin alkaloidini 1,2-dibrometan, 1,3-dibrompropan, 1,4-dibrombutan va 1,5-dibrompentanlar bilan reaksiyalari.

Sitizin – alkaloid bo‘lib, molekulasida ikkilamchi amin (–NH–) guruhi mavjud. Aynan shu azot atomi nukleofil markaz hisoblanadi. Shuning uchun sitizin alkilgalogenidlar bilan oson reaksiyaga kirishadi. Sitizin digalogenalkanlar bilan reaksiyasi S_N2 mexanizm bo‘yicha boradi. Bir bosqichli nukleofil almashinish, Br^- yaxshi chiqib ketuvchi guruh

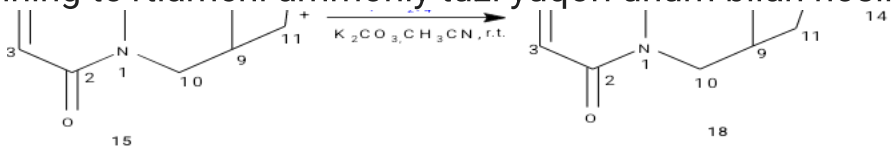
hisoblanadi. Avval monoalkillanish, keyin esa sharoitga qarab ichki halqalanish hosil bo‘lishi mumkin. Sitizinning 1,2-dibrometan, 1,3-dibrompropan, 1,4-dibrombutan, 1,5-dibrompentanlar bilan reaksiyalari olib borildi. Ushbu tajribalardan faqat 1,4-dibrombutan bilan olib borilgan tajribada bir bosqichda ichki sikillanish jarayoni yuz berib to‘rtlamchi ammoniy tuzi hosil bo‘ldi.



3-sxema. Sitizinning dibromalkanlar bilan reaksiya tenglamasining umumiy ko‘rinishi.

Bu yerda N-(2-brometil)sitizin (**16**), N-(3-brompropil)sitizin (**17**), N-(4-brombutan)sitizin (**18**), N-(5-brompentil)sitizin (**19**).

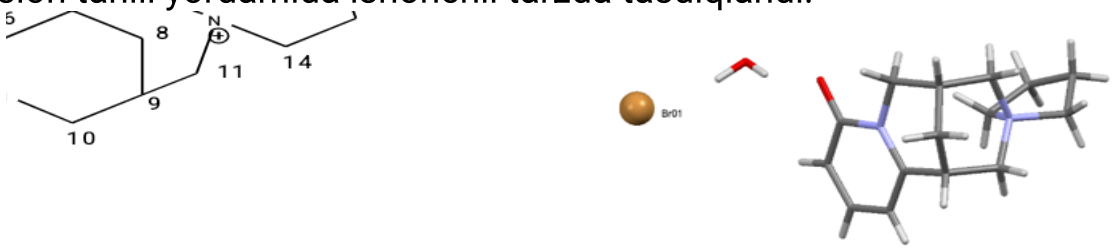
Nazariy ma’lumotlarga ko‘ra sitizin alkaloidi bilan reaksiyaga kirishgan to‘rtala dibromalkanlarda xam yuqoridagi reaksiya tenglamasida ko‘rsatilganidek, uchlamchi aminlar hosil bo‘lishi lozim edi. Ammo tajribalar natijasi shuni ko‘rsatdiki, 1,4-dibrombutan bilan olib borilgan tadqiqotda sitizinning to‘rtlamchi ammoniy tuzi yuqori unum bilan hosil bo‘ldi.



4-sxema. Sitizinning 1,4-dibrombutan bilan reaksiya tenglamasi.

Bu tuzning molekulyar va kristall tuzilishirentgen difraksiyasi usuli yordamida aniqlangan. Olingan natijalar moddaning to‘rtlamchi ammoniy tuziga xos bo‘lgan fazoviy tuzilishga ega ekanligini tasdiqlaydi. Rentgen tuzilish tahlili natijalariga ko‘ra, sitizin molekulasining tuzilishi o‘zining klassik uch o‘lchamli konformatsiyasini saqlab qolgan. Karbonil C=O bog‘i tekislikka yaqin holatda joylashgan bo‘lib, karbonil uglerod va unga tutash atomlar orasidagi bog‘ uzunliklari odatiy qiymatlarga mos keladi. Bu holat sitizin yadrosining alkillash jarayonida strukturaviy buzilishga uchramaganini ko‘rsatadi. Azot atomi to‘rtlamchi ammoniy markaz sifatida qatnashib, sitizin molekulasi va 1,4-butilen fragmenti bilan bog‘langan. Azot atomi atrofida birikmaning fazoviy shakli tetraedrik bo‘lib, bu
N-atomning musbat zaryadlangan holatiga mos keladi. Rentgen tuzilish tahliliga ko‘ra, 1,4-butilen fragmenti cho‘zilgan zig-zag (anti) konformatsiyada joylashgan. $-CH_2-CH_2-CH_2-CH_2-$ zanjiri sitizin yadrosiga nisbatan tashqi tomonga yo‘nalgan bo‘lib, sterik to‘siqlarni minimallashtiradi. Butilen zanjirining bunday joylashuvi molekulada ichki kuchlanishlarning kamayishiga olib keladi va birikmaning termodinamik

barqarorligini ta’minlaydi. Kristall tuzilishda Br^- anioni to‘rtlamchi ammoniy kationiga yaqin joylashgan bo‘lib, ular orasida kuchli elektrostatik tortishuv mavjud. Bromid anioni azot atomi yaqinida joylashib, kristall panjaraning barqarorligini oshiradi. Bundan tashqari, kristall tuzilishda quyidagi zaif o‘zaro ta’sirlar kuzatiladi: $N^+–H\cdot\cdot Br^-$ tipidagi ion-vodorod bog‘lanishlar, $C–H\cdots Br^-$ tipidagi ikkilamchi o‘zaro ta’sirlar. Mazkur o‘zaro ta’sirlar kristall panjarada molekulalarning muntazam joylashuvini ta’minlab, zich uch o‘lchamli struktura hosil qiladi. Kristall panjarada kationlar va anionlar qatlamli tarzda joylashgan bo‘lib, musbat va manfiy zaryadlarning almashinib kelishi umumiy elektrostatik barqarorlikni ta’minlaydi. Sitizin yadrolari orasida aromatik π–π stacking (ikki yoki undan ortiq aromatik halqa bir-biriga deyarli parallel holatda ustma-ust yaqinlashib joylashishi) kuzatilmaydi, bu esa molekulalarning fazoviy jihatdan hajmli va egri tuzilishga ega ekanligi bilan izohlanadi. Rentgen tuzilish tahlili natijalari quyidagilarni aniq tasdiqlaydi. Sitizin molekulasi alkillash jarayonida saqlanib qolgan. Azot atomi to‘rtlamchi ammoniy markaz sifatida qatnashadi. 1,4-butilen fragmenti cho‘zilgan konformatsiyada joylashgan. Bromid anioni kation bilan ion juftlik hosil qiladi. Kristall birikma ion-vodorod bog‘lanishlar orqali barqarorlashgan. Shu asosda sintez qilingan moddaning tuzilishi sitizinning to‘rtlamchi ammoniy tuzi ekanligi rentgen difraksion tahlil yordamida ishonchli tarzda tasdiqlandi.



4-rasm. Sitizinning to‘rtlamchi ammoniy tuzining kristalldagi tuzilishi va struktura formulasi.

Shu asosda sintez qilingan moddaning tuzilishi sitizin to‘rtlamchi tuzi ekanligi rentgen tuzilish tahlili yordamida ishonchli tarzda tasdiqlandi.

6-jadval

Sitizin hosilalarining reaksiya natijasida olingan mahsulot unumlari (Sitizin: dibromalkan: K_2CO_3: CH_3CN)

№	Olingan mahsulotlar	Reagentlarning mol nisbati	Vaqt, soat	Rf qiymati	Mahsulot unumi, %
1	N-(2-brometil) sitizin	1:1,5	6	0,65	96
2	N-(3-brompropil) sitizin	1:1,5	5	0,68	63
3	Sitizinning to‘rtlamchi ammoniy tuzi	1:1,5	4	0,25	95
4	N-(5-brompentan) sitizin	1:1,5	7	0,83	61

Reaksiyalar dastlabki moddalar mol nisbati turlicha ya’ni 1:1, 1:1.1, 1:1.2, 1:1.5 bo‘lgan nisbatlarda, erituvchining qaynash haroratida, turli hil

vaqt davomiyligida olib borildi. Jadvaldagi ma’lumotlarga ko‘ra, reagentlar mol nisbati 1:1.5 bo‘lganda, reaksiya davomiyligi 4-7 bo‘lganda maqbul sharoit deb topildi. Bu jarayon klassik organik kimyodagi halqa hosil bo‘lish termodinamikasi (Bayer kuchlanishlar nazariyasi) va entropiya qonuniyatlari bilan to‘liq asoslanadi.

Sitizin 1,4-dibrombutan bilan reaksiyaga kirishganda, birinchi alkillanishdan so‘ng qolgan bromalkil xuddi shu azotga qayrilib 5 a’zoli halqa hosil qiladi. 5 a’zoli halqalar termodinamik jihatdan eng kam kuchlanishga ega va eng barqaror strukturalardir, shuning uchun bu reaksiya kinetik jihatdan juda tez va oson (95 % unum bilan) boradi. 1,2-dibrometan holatida esa ichki sikllanish o‘ta kuchlanishli 3 a'zoli halqa hosil qilishni talab etganligi uchun jarayon qat'iy ravishda faqat toza monoalkillanish bosqichida to‘xtaydi va bu ham barqaror oraliq mahsulotni yuqori unumda (96 %) beradi. Biroq 1,3-dibrompropan va 1,5-dibrompentan ishtirok etganda jarayon ancha qiyinlashadi. 1,3-zanjir sikllanishga harakat qilsa, sterik to‘siqli va kuchlanishli 4 a’zoli halqa yuzaga keladi. 1,5-dibrompentanning uglerod zanjiri esa haddan tashqari uzun va moslashuvchan, molekula ichida bukilib (ichkimolekulyar) sikllanishigacha bo‘lgan entropik to‘siq juda yuqori bo‘ladi. Bu holat reaksiya tezligini kamaytirib, yon reaksiyalarni (masalan, ikkita alohida sitizin molekulasini bog‘lab qo‘yuvchi molekulalararo polimerlanishni) keltirib chiqaradi va maqsadli mahsulot unumini keskin kamaytirib (61-63%) yuboradi.

Dissertatsiyaning **“Sintez qilingan moddalarning biologik xossalari”** deb nomlangan uchinchi bobida tadqiqot natijasida olingan moddalarning antibakterial va antifungial faolliklari keltirilgan. Laboratoriya tadqiqotlari O‘simlik moddalari kimyosi institutining “Molekulyar genetika” (laboratoriya mudiri Azimova Sh.S.) laboratoriyasida amalga oshirilgan.

Antibakterial faolligi

Sintez qilingan birikmalarning mikroblarga qarshi faolligi Gram-musbat bakteriyalar (Bacillus subtilis, Staphylococcus aureus), Gram-manfiy bakteriyalar (Escherichia coli, Pseudomonas aeruginosa) hamda Candida albicans zamburug‘iga nisbatan disk-diffuziya usulida o‘rganildi. Tadqiqot natijalari shuni ko‘rsatdiki, tekshirilgan birikmalar orasida 4-benzil-4-nonilmorfoliniy xlorid (**10**) va 4-benzil-4-allilmorfoliniy xlorid (**11**) nisbatan yuqori antimikrob faollikka ega bo‘lib, ayniqsa, Bacillus subtilis ga qarshi mos ravishda 18 mm va 16 mm ingibirlanish zonalarini hosil qildi. Bundan tashqari, 4-benzil-4-allilmorfoliniy xlorid (11) Candida albicans ga nisbatan 15 mm ingibirlanish zonasini namoyon etib, zamburug‘larga qarshi faollik ko‘rsatdi. Ayniqsa, molekuladagi benzil va uzun alkil radikallarining mavjudligi hujayra membranasi bilan o‘zaro ta’sirni kuchaytirishi natijasida mikroorganizmlar o‘sishini samaraliroq ingibirlashga xizmat qilishi mumkin. Faollik darajasi standart preparatlar (Ampicillin/Sulbactam, Gentamicin va Fluconazole) bilan solishtirilganda pastroq bo‘lsa-da, ayrim birikmalarning

Gram-musbat bakteriyalar va zamburug‘larga nisbatan sezilarli ta’sir ko‘rsatishi ularni istiqbolli biologik faol moddalar sifatida keyingi farmakologik tadqiqotlar uchun tavsiya etish imkonini beradi.

7-jadval

4-Benzil-4-Nonilmorfoliniy xlorid (10), 4-Benzil-4-Allilmorfoliniy xlorid (11) va N-(5-brompentil) sitizin (19) larning antibakterial faolligi

Mahsulotlar	Ingibirlanish zonasi diametri (mm)				
	Gram-musbat bakteriyalar		Gram-manfiy bakteriyalar		Zamburug‘
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
4-Benzil-4-Nonilmorfoliniy xlorid (10)	18	8	6	6	N/A
4-Benzil-4-Allilmorfoliniy xlorid (11)	16	10	6	11	15
N-(5-brompentil)sitizin (19)	12	6	6	7	N/A
Ampicillin/ Sulbactam (10µg+10µg/disc)	24	20	-	-	-
Gentamicin (10 µg/disc)	-	-	19	22	-
Fluconazole (25 µg/disc)	-	-	-	-	26

Ingibirlash yo‘q – (N/A),
Kuchsiz ingibirlash zonasi ≤ 6 mm,
Seziladigan: 8–14 mm,
Yaqqol ko‘rinadigan: 14–20 mm,
Kuchli: ≥ 20 mm

Grammanfiy bakteriyalar tashqi membrana bilan himoyalangan bo‘lib, bu ularni antibiotik va boshqa kimyoviy moddalar ta’siriga nisbatan chidamliroq qiladi. Biroq E. coli ga nisbatan barcha birikmalarda bir xil 6 mm li ingibirlash maydonida antibakterial ta’sir ko‘rsatdi, P. aeruginosa esa nisbatan biroz kamroq sezgir bo‘lib, 6, 11, 7 mm ingibirlash maydonni qayd etdi. Candida albicans (15 mm) ham **(11)** birikmaga nisbatan sezgirlik namoyon etdi. Bu natija **(11)** birikmaning fungisitlik faollikka ham ega ekanligini ko‘rsatadi.

Dissertatsiyaning to‘rtinchi bobida tajribaviy qism, tadqiqot usullari, dastlabki birikmalar sintezi, ularni turli kimyoviy modifikatsiyalarini olib borish usullari keltirilgan. Birikmalarni identifikatsiya qilish va tuzilishini aniqlash usullari: xususan xromatografiya (YQX), spektroskopiya (IQ, ^{1}H va ^{13}C YMR-spektrlari) natijalari bayon qilingan.

XULOSA

1. Morfolinning turli alkilgalogenidlar, allil hamda propargilbromidlar bilan reaksiyalari olib borilib, tegishli N-alkil, N-allil, N-propargilmorfolinlar sintez qilindi. Alkilgalogenidlarda zanjiri uzunligining ortishi bilan mahsulot unumi yuqori bo‘lishi aniqlandi.

2. Ilk bor N-pentil-, N-nonil-, N-allil- va N-propargilmorfolinlarning benzil xlorid bilan o‘zaro ta’siridan 4-Benzil-4-Alkil(allil, propargil)morfoliniy xloridlar sintez qilinib, reagentlar mol nisbati 1:1,2, vaqt 5-7 soat, atsetonitril erituvchisi, reaksiyaning optimal sharoiti deb topilib, azot atomiga birikkan alkil va to‘yinmagan radikallarning reaksion faolligini tahlil qilinganda N-alkil hosilalarning reaksion qobiliyati quyidagi tartibda kamayib borishi N-allil morfolin> N-pentilmorfolin ≈ N-nonil morfolin > N-propargilmorfolin isbotlandi.

3. Sitizinning turli dibromalkanlar (1,2-dibrometan, 1,3-dibrompropan, 1,4-dibrombutan va 1,5-dibrompentan) ishtirokidagi sintezlari, sitizin molekulasidagi ikkilamchi azot atomi nukleofil markaz sifatida reaksiyaga kirishib, N-alkillangan mahsulotlarni hosil qildi. Reaksiya sharoitiga va dibromalkan zanjirining uzunligiga bog‘liq holda keyingi bosqichda molekula ichidagi nukleofil almashinish reaksiyasi sodir bo‘lib, yangi sikllangan hosila vujudga kelishi kuzatilib,reaksiya mexanizmi taklif qilindi.

4. 4-Benzil-4-Pentil-, 4-Benzil-4 Nonilmorfoliniy xlorid va sitizinning 1,4-dibrombutan bilan olingan hosilasining rombik va monoklinik tuzilishga ega bo‘lgan kristallari rentgen tuzilish tahlili aniqlanib, Xalqaro Kembrij kristallografik ma’lumotlar bazasiga kiritildi.

5. Sintez qilingan moddalardan 4-Benzil-4-Nonilmorfoliniy xlorid, 4-Benzil-4-Allilmorfoliniy xlorid va N-(5-brompentil) sitizinning *Bacillus subtilis, Staphylococcus aureus* grammusbat, *Escherichia coli, Pseudomonas aeruginosa* grammanfiy bakteriyalarga qarshi bakterisidlik, shuningdek, *Candida albicans* patogen zamburug‘larga qarshi fungisidlik faolliklarini namoyon qilishi aniqlandi.

SCIENTIFIC COUNCIL No. DSc.03/2025.27.12.K.01.13.M FOR THE AWARD OF ACADEMIC DEGREES AT NATIONAL UNIVERSITY OF UZBEKISTAN

NATIONAL UNIVERSITY OF UZBEKISTAN

YAKHSHILIKOVA ZARIFA ABDIMANNONOVNA

ALKYLATION OF CYTISINE AND MORPHOLINE AND SYNTHESIS BASED ON THEIR ALKYL DERIVATIVES

02.00.03 – Organic Chemistry

DOCTOR OF PHILOSOPHY IN CHEMICAL SCIENCES (PhD)
ABSTRACT OF THE DISSERTATION

Tashkent – 2026

The theme of the Doctor of Philosophy (PhD) dissertation was registered in the Higher Attestation Commission under the Ministry of Higher Education, Science and Innovation of the Republic of Uzbekistan under number **B2024.2PhD/K761**.

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Scientific supervisor:	**Kholikov Tursunali Suyunovich** doctor of Chemical Sciences, professor
Official opponents:	**Makhsumov Abdulkhamid Gafurovich** doctor of Chemical Sciences, professor
	Matchanov Alimjon Davletbayevich doctor of Chemical Sciences, professor
Leading organization:	**Tashkent pharmaceutical institute**

The dissertation defense will take place at the meeting of the Scientific Council DSc.03/2025.27.12.K.01.13.M at the National University of Uzbekistan on «___» _____ 2026 at ____ (Tashkent, University Street, 4).

The dissertation can be reviewed at the Information Resource Center of the National University of Uzbekistan (registered under No. ___) (Tashkent, University Street, 4).

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M.A. Makhkamov
Deputy chairman Scientific Council for
Awarding Academic Degrees
Doctor of Chemical Sciences, Professor

U.O. Ruzmetov
Scientific Secretary of the Scientific Council
for Awarding Academic Degrees
Doctor of Chemical Sciences, Professor

A.K. Abdushukurov
Chairman of the Scientific Seminar
under the Scientific Council for Awarding
Academic Degrees, Doctor of Chemical Sciences, Professor

INTRODUCTION
(Annotation of the PhD Dissertation)
Relevance of the dissertation topic.

Today, morpholine and cytisine derivatives are widely used worldwide in medicine and pharmaceuticals as therapeutic agents against various diseases, as well as in the agro-industrial sector as herbicides and fungicides. Morpholine derivatives are utilized in the form of pharmaceutical preparations such as the antibiotic linezolid, the antidepressant reboxetine, the antifungal agent amorolfine for the treatment of skin and nail fungal infections, and the anticancer drug gefitinib. Cytisine-based preparations, particularly Tabex, are widely employed as smoking cessation agents. Therefore, the development of analogs of these pharmaceuticals, the improvement of their synthetic methods, and their practical application are of significant scientific and practical importance.

Extensive research is currently being conducted worldwide to develop efficient methods for the synthesis of N-alkyl derivatives of morpholine and cytisine, as well as to propose new catalysts for these alkylation reactions. In particular, the synthesis of quaternary ammonium compounds through the alkylation of N-alkyl-, N-allyl-, and N-propargylmorpholines—obtained via the alkylation of morpholine with alkyl, allyl, and propargyl halides—and through the alkylation of cytisine with dibromoalkanes in the presence of benzyl chloride represents a scientifically important research direction.

In recent years, significant achievements have been made in the Republic of Uzbekistan in the field of scientific research aimed at expanding existing knowledge, ensuring the integration of research commercialization with industrial development, and producing import-substituting products based on local raw materials through the synthesis of natural and synthetic organic compounds. The Development Strategy of the New Uzbekistan for 2022–2026 outlines the task of “continuing industrial policies aimed at ensuring the stability of the national economy and increasing the share of industry in the gross domestic product, thereby increasing industrial production volume by 1.4 times.” In this context, the determination of optimal conditions for the synthesis of quaternary ammonium compounds via alkylation reactions of nitrogen-containing

heterocyclic compounds, the structural characterization of the synthesized compounds using modern physicochemical methods, the identification of key factors and reaction regularities affecting reaction yields, the investigation of physicochemical and biological properties of the obtained compounds, and the expansion of research aimed at developing biologically active substances containing various functional groups are considered highly important scientific objectives.

This dissertation research also contributes, to a certain extent, to the implementation of the tasks specified in the Resolution of the President of the Republic of Uzbekistan No. PQ-3983 dated October 25, 2018, “On Measures for the Accelerated Development of the Chemical Industry of the Republic of Uzbekistan”; Resolution No. PQ-4265 dated April 3, 2019, “On Further Reforming the Chemical Industry and Increasing Its Investment Attractiveness”; Resolution No. PQ-4805 dated August 12, 2020, “On Measures to Improve the Quality of Continuous Education and the Effectiveness of Scientific Research in the Fields of Chemistry and Biology”; as well as other regulatory and legal documents related to this area of activity.

Compliance of the Research with Priority Areas of Science and Technology Development of the Republic. This research has been carried out in accordance with the priority areas of science and technology development of the Republic, specifically Priority Area VII — “Chemical Sciences, Chemical Technologies, and Nanotechnologies.”

Degree of Study of the Problem. Alkylation reactions of heterocyclic compounds have been extensively studied in the field of organic chemistry in many developed countries around the world. In particular, leading international scientists have conducted research aimed at the synthesis of target compounds. A. Coe, J. L. Stolerman, and R. A. Clarke carried out fundamental studies on the interaction of cytisine with nicotinic receptors and on its structural analogues. I. D. M. Toth and J. R. Livingstone investigated the structure–activity relationships of cytisine and its N-alkyl derivatives. H. R. Snyder and R. Adams studied the alkylation reactions of nitrogen-containing heterocycles, including morpholine, from the perspective of classical organic chemistry. European schools of pharmaceutical chemistry have focused on the synthesis of N-alkylated morpholine derivatives and quaternary ammonium salts, as well as the evaluation of their biological activities.

In the Republic of Uzbekistan, a number of leading scientists have conducted research on the synthesis of quaternary ammonium compounds based on morpholine and cytisine, as well as on alkylation reactions involving alkyl, allyl, and propargyl halides. In particular, S. Yu. Yunusov and his colleagues, Sh. B. Rakhimov, V. I. Vinogradova, A. G. Maksumov, H. S. Tojimuhamedov, O. Sh. Xoliqova, O. S. Maksumova, and others isolated cytisine from plant sources and carried out extensive investigations on its

derivatives, as well as on the synthesis and chemical properties of morpholine derivatives.

A review of the scientific literature indicates that, despite the availability of extensive experimental data on the synthesis of N-alkyl derivatives of morpholine and cytisine, compounds such as N-allyl(propargyl)-N-benzyl derivatives, N-alkyl-N-benzyl morpholine derivatives, and certain N-alkyl cytisine derivatives remain insufficiently studied. Therefore, investigating their reactions with alkyl halides and dihaloalkanes, as well as evaluating the biological activity of the synthesized compounds, is of considerable scientific interest. Accordingly, the present dissertation research is aimed at investigating the nucleophilic substitution reactions of N-alkylmorpholines, obtained through the alkylation of morpholine, with benzyl chloride, and at carrying out the targeted synthesis of biologically active cytisine derivatives in reactions involving dibromoalkanes.

Relationship of the research to the scientific research activities of the institution where the dissertation was carried out. The dissertation has been performed within the framework of the fundamental research project of the National University of Uzbekistan, AM-FZ-2019081452, entitled “Development of Cyclohexane Synthesis Technology Based on Ethylene” (2020–2022).

Aim of the research. The objective of this research is to perform the alkylation of cytisine and morpholine and to synthesize novel compounds based on the obtained alkylated derivatives.

Research tasks.

To investigate the reactions of morpholine with various alkylating reagents (monoalkyl halides) and to determine the dependence of the alkylation reactions on the nature of the alkylating agent;

To carry out nucleophilic substitution reactions of the synthesized N-pentyl-, N-nonyl-, N-allyl-, and N-propargylmorpholines with benzyl chloride;

To elucidate the N-alkylation and intramolecular cyclization processes occurring in the reactions of cytisine with various dibromoalkanes;

To confirm the structures of the newly synthesized compounds using modern physicochemical methods, including IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy, and X-ray crystallographic analysis;

To evaluate the biological activity of the obtained cytisine derivatives and morpholine-based quaternary ammonium salts against Gram-positive and Gram-negative bacteria, as well as fungi, under in vitro conditions.

Objects of the research. The objects of this research were cytisine and morpholine, alkylating agents, their alkylated derivatives, and the corresponding quaternary ammonium salts.

Subject of the research. The subject of this research comprises the alkylation reactions of cytisine and morpholine, the mechanistic pathways

of these processes, including S_N2 substitution and intramolecular cyclization reactions, the formation regularities and molecular structures of the resulting alkyl derivatives and quaternary ammonium salts as a function of reaction conditions, and the study of their physicochemical properties.

Research methods. The research methods included thin-layer chromatography (TLC), IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, X-ray crystallographic analysis (XRD), and methods for the evaluation of biological activity.

Scientific novelty of the research.

In the reactions of morpholine with monohaloalkanes, it was established that the product yield increases with the elongation of the alkyl chain in the order N-butylmorpholine<N-pentylmorpholine < N-hexylmorpholine < N-nonylmorpholine.

The higher yields obtained under SN2 reaction conditions in ethanol at 78 °C were explained by the influence of solvent nature and reaction temperature on the reaction efficiency.

For the first time, quaternary ammonium salts, namely 4-benzyl-4-pentylmorpholinium chloride, 4-benzyl-4-nonylmorpholinium chloride, 4-benzyl-4-allylmorpholinium chloride, and 4-benzyl-4-propargylmorpholinium chloride, were synthesized through the reactions of N-alkyl-, N-allyl-, and N-propargylmorpholines with benzyl chloride in acetonitrile. It was demonstrated that the highest reaction yield (96%) was achieved at an N-allyl (or N-propargyl)morpholine to benzyl chloride molar ratio of 1:1.2.

During the alkylation of cytisine, the intramolecularly cyclized compound N-(1,4-butylene) quaternary cytisine bromide was synthesized in a single step. The formation of a stable cyclic structure with an orthorhombic crystal system ($\alpha = \beta = \gamma = 90°$) was established, and the compound was obtained in 95% yield.

Based on N-hexylmorpholine, 4-hexyl-4-nonylmorpholinium bromide was synthesized in the presence of iron(III) chloride as a catalyst. The results demonstrated the catalytic activity of this Lewis acid in the alkylation process.

The absence of the characteristic N–H stretching vibrations of morpholine in the 3300–3400 cm^{-1} region and the appearance of aliphatic C–H absorption bands in the 2850–2960 cm^{-1} region in the IR spectra of N-alkyl-, N-allyl-, and N-propargylmorpholines confirmed their tertiary amine nature. In the ^1H NMR spectra, signals corresponding to the methylene group attached to the nitrogen atom (H-7) were observed at δ 2.20–2.35 ppm. The crystal structure of 4-benzyl-4-nonylmorpholinium chloride was determined by X-ray crystallographic analysis, confirming its crystallization in the monoclinic crystal system with unit-cell parameters a = 8.7990(5) Å, b = 7.4720(4) Å, c = 32.998(2) Å, and β = 95.561(3)°.

Practical results of the research. It was demonstrated that reactions

of tertiary amines derived from morpholine with benzyl chloride can be efficiently carried out in various solvents, leading to the corresponding quaternary ammonium salts in high yields.The molecular geometry and complete crystallographic parameters of the synthesized quaternary ammonium salts, specifically 4-benzyl-4-pentylmorpholinium and 4-benzyl-4-nonylmorpholinium derivatives, as well as the cytisine-derived compound formed with 1,4-dibromobutane, were determined and confirmed. The obtained structural data were deposited in the Cambridge Crystallographic Data Centre (CCDC) and may be used as a reference for the synthesis and structural comparison of similar compounds.

It was further established that 4-benzyl-4-nonylmorpholinium chloride and N-(5-bromopentyl)cytisine exhibit bactericidal activity against Gram-positive bacteria (Bacillus subtilis, Staphylococcus aureus) and Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa), while 4-benzyl-4-allylmorpholinium chloride demonstrated fungicidal activity against the pathogenic fungus Candida albicans.

Reliability of the research results. The research results were confirmed on the basis of spectral methods (NMR and IR spectroscopy), X-ray crystallographic analysis (XRD), chromatographic methods (TLC), and biological evaluation methods. The reliability of the obtained results is further supported by their publication in peer-reviewed international scientific journals.

Scientific and practical significance of the research results.
The scientific significance of the research lies in the fact that the alkylation of the cytisine alkaloid and morpholine, as well as the first-time synthesis of quaternary ammonium salts based on N-alkyl products, and the one-step synthesis of an intramolecularly cyclized cytisine-derived compound, have been achieved. In addition, the determination of composition, structure, properties, and stability of the synthesized compounds, together with the conclusions drawn based on modern physicochemical analytical methods, has contributed to enriching the theoretical framework of heterocyclic chemistry with new data and materials.

The practical significance of the research is reflected in the successful growth of single crystals of 4-benzyl-4-pentylmorpholinium and 4-benzyl-4-nonylmorpholinium salts, as well as the cytisine derivative formed with 1,4-dibromobutane. Their spatial structures and complete crystallographic parameters were determined and confirmed, and the obtained data were deposited in the Cambridge Crystallographic Data Centre (CCDC).

It was further demonstrated that 4-benzyl-4-nonylmorpholinium chloride, 4-benzyl-4-allylmorpholinium chloride, and N-(5-bromopentyl)cytisine exhibit significant antibacterial and antifungal activity against bacteria and fungi at certain concentrations. The study confirms the successful synthesis of biologically active compounds based on

cytisine and morpholine and demonstrates the feasibility of obtaining a range of new compounds efficiently through reactions with various alkylating reagents.

Implementation of Research Results.

Based on the scientific results obtained in the synthesis and chemical modification of new quaternary ammonium salts derived from N-pentylmorpholine, N-nonylmorpholine, and cytisine, the crystal structures of three compounds were determined. The corresponding structural data were deposited in the Cambridge Structural Database (The Cambridge Crystallographic Data Centre, https://www.ccdc.cam.ac.uk) under the identification numbers CCDC: 2277070, 2541862, and 2541863. This has enabled comparative studies of spatial structures and facilitated the synthesis and structural analysis of related compounds.

The obtained results were also applied within the framework of the fundamental project FL–7923051904 entitled “Synthesis, Structure, and Electronic Properties of Nanostructured Catalysts and Their Supports for the Preparation of Vinyl Compounds” (2024–2025), carried out at the National University of Uzbekistan and supported by the Innovation Development Agency under the Ministry of Higher Education, Science and Innovation of the Republic of Uzbekistan (reference No. 01-02/1/1677, dated April 22, 2026). As a result, methodological approaches for the synthesis of new compounds, as well as for the determination of their crystal structures and physicochemical properties, were further developed. The obtained scientific results also provide opportunities for application in the design of promising functional materials and in the evaluation of their properties.

Approbation of the research results. The findings of this research were reported and discussed at seven scientific and practical conferences, including two international and five national-level conferences.

Publication of the research results. A total of 11 scientific publications have been published on the topic of the dissertation. Four articles were published in scientific journals recommended by the Higher Attestation Commission of the Republic of Uzbekistan for the publication of the main scientific results of PhD dissertations, including one article in an international Scopus-indexed journal and three articles in national journals.

Structure and volume of the dissertation. The dissertation is structured into an introduction, three chapters, a conclusion, a list of references, and appendices. The total length of the dissertation comprises 110 pages[2].

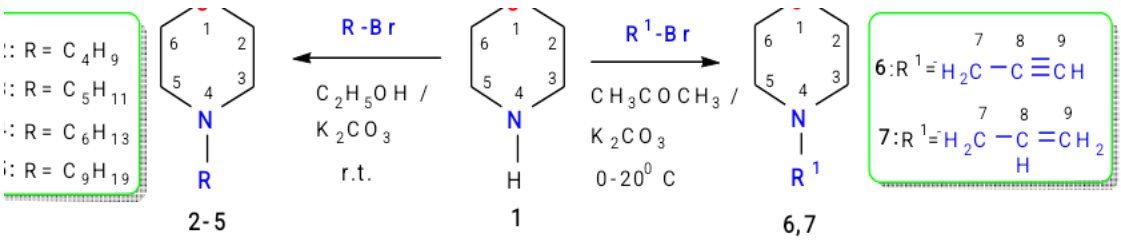
MAIN CONTENT OF THE DISSERTATION

The introduction provides information on the relevance and necessity of the conducted research, its aim and objectives, as well as the description

of the object and subject of the study. It also demonstrates the compliance of the research with the priority directions of science and technology development of the Republic, outlines the scientific novelty and practical significance of the obtained results, and describes their implementation in practice. In addition, information on published works and the structure of the dissertation is presented. The first chapter of the dissertation, entitled **"Synthesis of quaternary ammonium salts based on morpholine and cytisine,"** presents a literature review. It analyzes data on morpholine-based syntheses, cytisine-based syntheses, as well as the preparation and properties of quaternary ammonium salts. The current state of research related to their synthesis, modification, and biological activity is also critically reviewed.

The second chapter of the dissertation, entitled **"Synthesis of N-alkylmorpholines and the preparation of quaternary ammonium salts based on them, as well as the synthesis of various cytisine derivatives via reactions with dibromoalkanes",** presents the results of the research.

The results of studies on the reactions of morpholine with butyl, pentyl, hexyl, and nonyl bromides are presented in detail, including the optimization of reaction conditions such as solvent type, temperature, reagent ratios, and reaction time. In addition, the influence of alkyl chain length on reactivity and product yield was comparatively analyzed, and optimal conditions were identified. The influence of various factors such as solvent nature, reaction time, and reagent characteristics on product yield in the reactions of morpholine with alkyl halides was investigated. Ethanol and acetone were used as solvents. The obtained results are presented below.



Scheme 1. Reactions of morpholine with saturated and unsaturated alkyl bromides

The author expresses sincere gratitude to Sh. N. Jo'raqulov, Leading Researcher at the Institute of the Chemistry of Plant Substances of the Academy of Sciences of the Republic of Uzbekistan, for his valuable assistance in carrying out this dissertation research.

Table 1.
Effect of reaction time and solvent on the yield of morpholine reactions with alkyl halides (Morpholine : alkyl halide : K_2CO_3 = 1:1:1).

№		Product yield (%) and reaction time (hours)

	Reagents 1:1:1	1 hour		3 hour		4 hour		5 hour		7 hour	
		acetone	ethanol	acetone	ethanol	acetone	ethanol	acetone	ethanol	acetone	ethanol
2	Morpholine:Butyl bromide:K_2CO_3	50	52	50	55	60	68	60	68	-	-
3	Morpholine:Butyl bromide:K_2CO_3	66	75	70	81	70	81	-	-	-	-
4	Morpholine:Butyl bromide:K_2CO_3	43	52	59	68	74	82	74	82	-	-
5	Morpholine:Butyl bromide:K_2CO_3	42	51	53	62	65	70	67	74	78	86

An increase in the length of the carbon chain positively influences the product yield through several thermodynamic and kinetic factors. First, as the alkyl chain length increases (from butyl bromide to nonyl bromide), the boiling point of the alkyl halides increases significantly, while their volatility decreases. Since the reaction is carried out under reflux conditions for 5–7 hours, a portion of short-chain reagents (e.g., butyl bromide) may be lost from the reaction medium due to evaporation. In the case of heavier reagents such as nonyl bromide, such losses are practically negligible, and the effective concentration remains high.

Secondly, in long-chain (unbranched) primary alkyl halides, steric hindrance at the α-carbon atom is almost similar regardless of chain length (as both are accessible for S_N2 attack), however, the higher lipophilicity of nonyl bromide contributes to greater stability of intermediate complexes in the organic phase, which leads to an experimentally observed increase in reaction yield up to 86%.

From a theoretical perspective, polar aprotic solvents (such as acetone) are considered optimal for such reactions because they do not strongly solvate nucleophiles, thereby increasing their reactivity. Accordingly, higher reaction rates and yields are generally expected in acetone media.

However, the experimental results of this study favor ethanol, which can be explained by thermodynamic temperature effects and the physical properties of the solvents. The boiling point of acetone is relatively low (56 °C), whereas that of ethanol is higher (78 °C). Since the reactions were conducted under reflux at the boiling point of the solvent, the reaction in ethanol proceeds at 78 °C, providing higher thermal (kinetic) energy to the reacting species. This significantly increases the probability of overcoming the activation energy (Ea) barrier of the SN2 process. As a result, the higher temperature overrides the advantages provided by the aprotic nature of acetone, and within the given reaction time (5 hours), ethanol ensures a noticeably higher product yield due to kinetic enhancement.

Therefore, the higher yield observed in ethanol compared to acetone is explained by a combination of physicochemical factors and is consistent

with the experimental results.

Table 2.

Yields and physicochemical properties of products obtained from the reactions of morpholine with alkyl halides

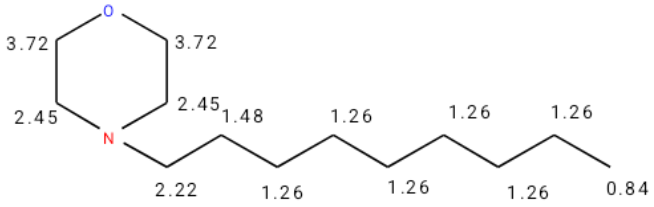
№	Obtained Product	Molar Ratio of Reagents	Time (h)	Rf Value	Product Yield (%)	Boiling Point (°C)	Physical State, Color
2	N-Butylmorpholine	1:1	4	0.71	68	178–182	Liquid, light yellow
3	N-Pentylmorpholine	1:1	3	0.77	81	195–200	Liquid, light yellow
4	N-Hexylmorpholine	1:1	5	0.69	82	215–220	Liquid, light yellow
5	N-Nonylmorpholine	1:1	7	0.66	86	270–280	Oily liquid, yellowish

In this work, a series of N-alkylmorpholines was synthesized based on alkylation reactions of morpholine with alkyl halides in a 1:1 molar ratio. N-butyl-, N-pentyl-, N-hexyl-, and N-nonylmorpholine derivatives were obtained, and their reaction kinetics, yield characteristics, and physicochemical properties were investigated using thin-layer chromatography (TLC).

As the alkyl chain length increases, steric hindrance becomes more pronounced, while the phase properties of the reagents (such as viscosity and diffusion rate) decrease, leading to a reduction in reaction rate. In particular, diffusion limitations play an important role in reactions involving C_6- and C_9-alkyl halides.

TLC analysis showed that all synthesized compounds exhibited an identical Rf value of 0.66-0,71. This indicates that, under the applied eluent system, the polarity of N-alkylmorpholines is very similar, and the main structural difference lies only in the length of the alkyl chain. The presence of the morpholine ring as a constant polar fragment accounts for the minimal variation in Rf values.

Overall, the obtained results demonstrate that the alkylation of morpholine with alkyl halides proceeds efficiently at 80 °C, that a 1:1 molar ratio is optimal, and that the synthesized N-alkylmorpholines can be obtained in high yields. The observed kinetic and thermodynamic закономерности confirm that this class of compounds is promising for applications in organic synthesis and surfactant chemistry.



Analysis of the ^1H and ^{13}C NMR spectra of N-nonylmorpholine

In the ^1H NMR spectrum of N-nonylmorpholine, in contrast to the starting morpholine, a distinct triplet signal (J = 7.1 Hz) was observed at δ 0.84

ppm, corresponding to the protons of the terminal methyl group (H-15, CH_3). In the region of δ 1.26 ppm, multiplet signals corresponding to the methylene protons of the nonyl chain (H-9, H-10, H-11, H-12, H-13, H-14, CH_2 groups) were detected. At δ 1.48 ppm, a triplet signal (J = 7.7 Hz) attributed to the methylene group H-8 was observed. In the region of δ 2.32 ppm, multiplet signals corresponding to the methylene group directly attached to the nitrogen atom of the morpholine ring (H-7, N–CH_2) were identified. The remaining signals were assigned to the characteristic protons of the morpholine moiety.

In the ^{13}C NMR spectrum, the signal at δ 14.18 ppm corresponds to the terminal methyl carbon (C-15) of the nonyl chain. Signals at δ 22.74 ppm, 26.43 ppm, 27.56 ppm, 29.34 ppm, 29.60 ppm, and 31.94 ppm were assigned to the methylene carbons of the alkyl chain (C-14, C-9, C-8, C-12, C -10/C-11, and C-13, respectively). The signal at δ 59.27 ppm corresponds to the carbon (C-7) of the methylene group attached directly to the nitrogen atom of the morpholine ring. The remaining carbon signals are attributed to the morpholine ring carbons, confirming the preservation of its structural framework.Overall, the NMR data unambiguously confirm the successful synthesis of nonylmorpholine and are in full agreement with the proposed molecular structure.

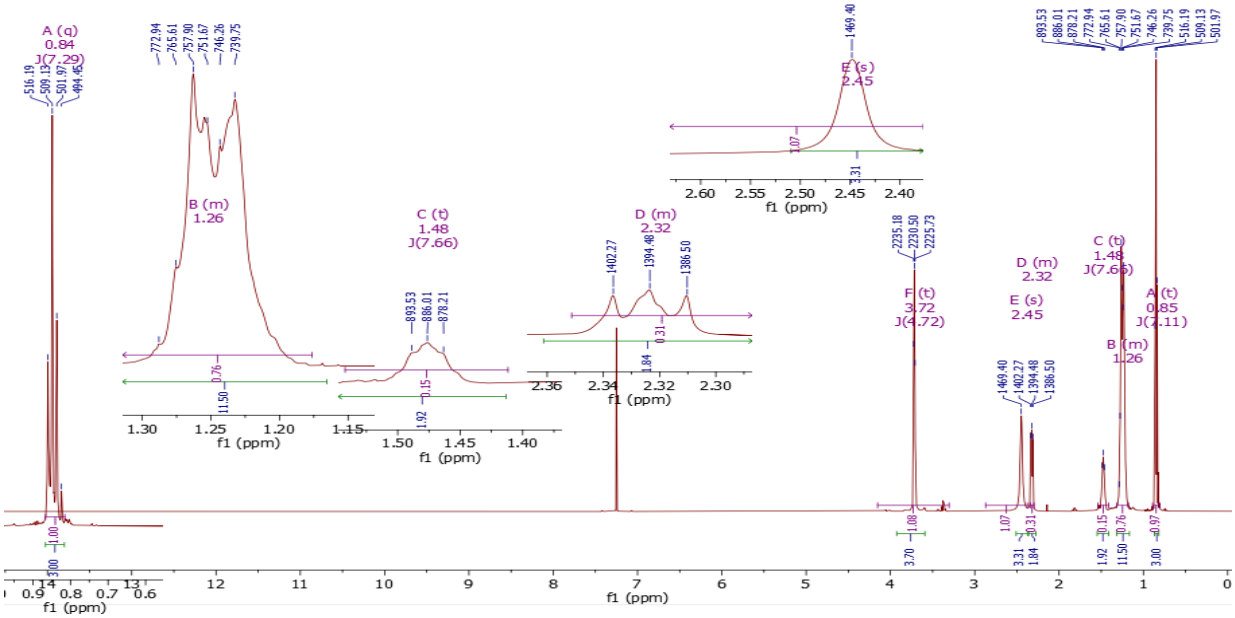


Figure 1. ^1H NMR spectrum of N-nonylmorpholine (5)

Table 3

Effect of reaction time on the yields of morpholine reactions with allyl and propargyl bromides (Morpholine : alkyl halide : K_2CO_3 = 1:1:1)

№	Reagents 1:1:1	Product yield (%) and reaction time (hours)			
		1 h	2 h	3 h	4 h

6	Morpholine:Butyl bromide:K_2CO_3	63	91	92	92
7	Morpholine:Butyl bromide:K_2CO_3	86	87	87	-

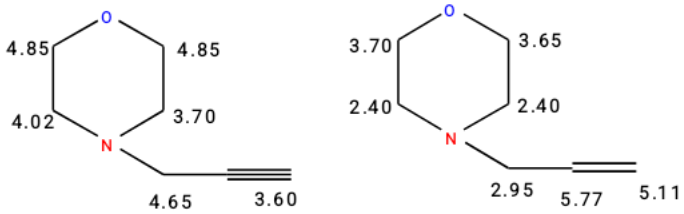
Morpholine was dissolved in acetone, after which allyl and propargyl bromides were added dropwise. The reaction mixture was stirred using a magnetic stirrer for 3-4 hours at room temperature to afford the desired products. The reactions of morpholine with unsaturated allyl and propargyl bromides can be optimized to increase the reaction yield by using an aprotic solvent such as acetone.

Table 4

Effect of reagent ratio on the yields of morpholine reactions with allyl and propargyl bromides (Morpholine : alkyl halide : K_2CO_3 = 1:1:1)

№	Reagents	Product yield (%) and molar ratio of reagents		
		1:1	1:1,1	1:1,2
6	Morpholine:Butyl bromide:K_2CO_3	91	92	92
7	Morpholine:Butyl bromide:K_2CO_3	86	87	87

Tables 3 and 4 present the results of studying the effect of reaction time and the ratio of initial reagents on the yield of reactions between morpholine and unsaturated alkyl bromides. The reactions were carried out at different molar ratios (1:1, 1:1.1, and 1:2) and at various time intervals 1 h, 2 h, 3 h and (4h N-propargylmorpholine). When the reagent ratio was 1:1, the highest yield was achieved with the shortest reaction time.



^1H and ^{13}C NMR spectral analysis of N-propargylmorpholine In the ^1H NMR spectrum of N-propargylmorpholine, in comparison with the starting morpholine, a characteristic triplet signal (J = 2.6 Hz) was observed at δ 3.60 ppm, corresponding to the proton of the terminal alkyne group (H-9, C≡CH). In the region of δ 3.70 and 4.02 ppm, multiplet and doublet of doublets signals (J = 5.9, 3.9 Hz) assigned to the methylene protons attached to the nitrogen atom of the morpholine ring (H-3 and H-5, N–CH_2) were detected. At δ 4.65 ppm, a signal corresponding to the methylene group of the propargyl fragment directly bonded to nitrogen (H-7, N–CH_2)

was observed. In addition, at δ 4.85 ppm, signals attributed to the methylene protons attached to the oxygen atom (H-2 and H-6, O–CH_2) were identified. In the ^{13}C NMR spectrum, the signal at δ 50.19 ppm corresponds to the carbon atom of the propargyl fragment attached to nitrogen (C-7). The signal at δ 69.69 ppm is assigned to C-9 (the terminal alkyne carbon bearing hydrogen), while the signal at δ 82.73 ppm corresponds to the internal sp-hybridized carbon atom of the triple bond (C-8). These spectroscopic data confirm the successful synthesis of N-propargylmorpholine and are in full agreement with its proposed molecular structure.

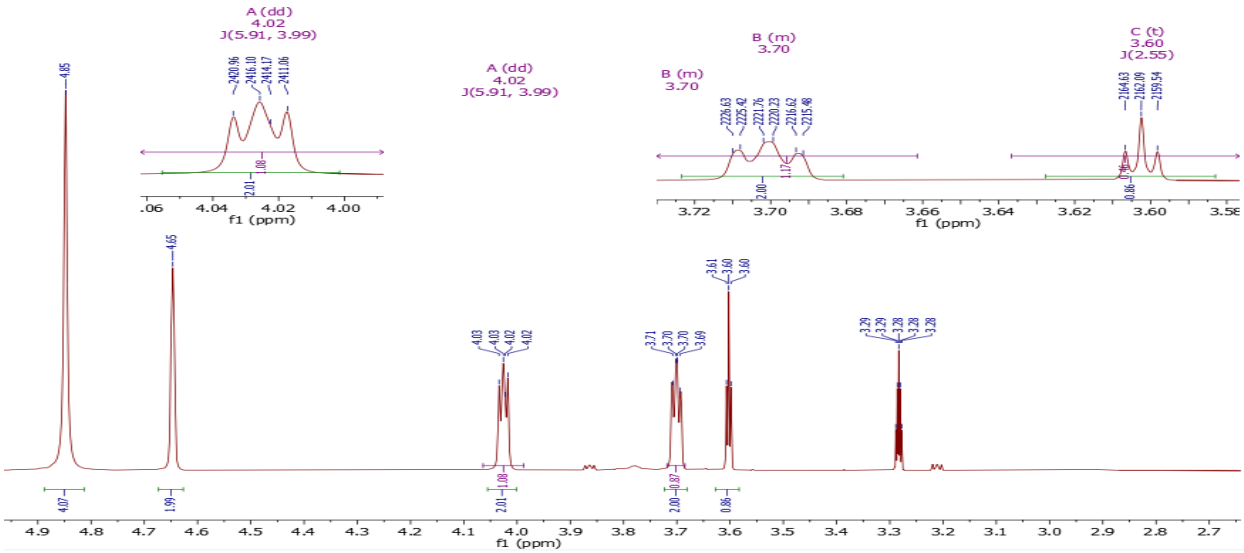
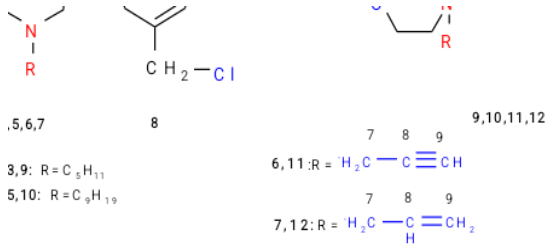


Figure 2. ^1H NMR spectrum of N-propargylmorpholine

The structures of the synthesized products obtained from the reactions of morpholine with unsaturated alkyl halides were analyzed using IR spectroscopy, ^1H NMR, and ^{13}C NMR spectroscopic methods.

Reactions of N-pentyl-, N-nonyl-, N-allyl-, and N-propargylmorpholine with benzyl chloride

Quaternary ammonium compounds possess surfactant, detergent, and antimicrobial properties. One of the most widely applied areas of these salts is sanitation and disinfection. It has been established that quaternary ammonium salts obtained based on morpholine exhibit complete disinfectant activity against *Staphylococcus aureus* ATCC 25923 and *Escherichia coli* ATCC 25922 bacteria. In addition, it is well known that most drugs containing a morpholine fragment exhibit biological activity.



Scheme 2. Synthesis of quaternary ammonium salts

In this scheme, N-pentylmorpholine (3), N-nonylmorpholine (5), N-propargylmorpholine (6), N-allylmorpholine (7), 4-benzyl-4-pentylmorpholinium (9), 4-benzyl-4-nonylmorpholinium (10), 4-benzyl-4-propargylmorpholinium (11), and 4-benzyl-4-allylmorpholinium (12) are presented. Based on the above experiments, quaternary ammonium salts were obtained in high yields through the reaction of N-alkylmorpholines with benzyl chloride under reflux conditions in a polar aprotic solvent (acetonitrile). The obtained results are presented in Table 5.

Table 5

Yields and physicochemical properties of newly synthesized quaternary ammonium salts

№	Obtained Product	Molar Ratio of Reagents	Time (h)	Melting Point (°C)	Rf Value	Product Yield (%)	Physical State, Color
9	4-Benzyl-4-Pentylmorpholinium Chloride	1:1.2	5.5	194–196	0.60	94	White crystals
10	4-Benzyl-4-Nonylmorpholinium Chloride	1:1.2	7.0	196–198	0.68	89	White crystals
11	4-Benzyl-4-Propargylmorpholinium Chloride	1:1.2	4.5	205–207	0.64	80	Brown, resinous
12	4-Benzyl-4-Allylmorpholinium Chloride	1:1.2	5.0	214–216	0.63	96	White powder

N-alkylmorpholines obtained from morpholine were further reacted with benzyl chloride at various molar ratios of 1:1, 1:1.1, 1:1.2, and 1:1.5. As a result, the highest yield was achieved at a 1:1.2 molar ratio. The experiments were carried out at different reaction times under reflux conditions in a polar aprotic solvent, and in particular, a high yield of 4-benzyl-4-pentylmorpholinium salt was obtained.

The tertiary nitrogen atom (R_3N) in the morpholine derivative possesses a lone electron pair and acts as a strong nucleophile, which attacks the electrophilic center of benzyl chloride. The C–Cl bond is cleaved and a new C–N bond is formed, resulting in the formation of N-

benzyl-N-alkylmorpholinium chloride (quaternary ammonium salts). The reaction proceeds via an SN2 nucleophilic substitution mechanism. In this process, the nature of the alkyl substituent significantly affects both the reaction rate and product yield. The N-pentyl and N-nonyl derivatives possess long alkyl chains, which increase steric hindrance and decrease reaction rate, although lipophilicity increases. In the N-allyl derivative, the presence of a π-system and electron-donating effects increases nucleophilicity, resulting in a faster reaction. In the N-propargyl derivative, the sp-hybridized carbon exerts a relatively stronger electron-withdrawing effect, which may reduce nucleophilicity. Thus, the reactivity order of N-alkyl derivatives decreases as follows:
N-allylmorpholine>N-pentylmorpholine≈N-nonylmorpholine>N-propargyl morpholine

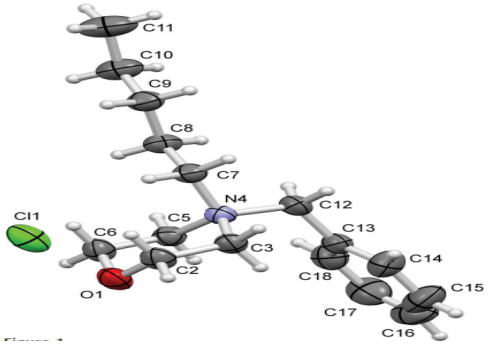
Acetonitrile (CH_3CN), used as the reaction solvent, is a polar aprotic solvent that does not strongly solvate nucleophiles, thereby accelerating the SN2 reaction and providing an optimal medium for quaternary ammonium salt formation. Benzyl chloride, as a highly reactive substrate, ensures high reaction yields.

Quaternary ammonium salts possess antimicrobial activity, are used as phase-transfer catalysts, and also have important practical significance in the synthesis of pharmaceutical drugs.

The reactions were monitored by TLC (chloroform:methanol system: 16:1, 12:1, 4:1, 2:1), and Rf values of the synthesized compounds were determined.The structures of the synthesized compounds were confirmed by IR, ^1H and ^{13}C NMR spectroscopy, and X-ray crystallographic analysis (Figure 3).

^1H NMR (600 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87 (3H, t, J = 6.19, H-11), 1.33 (4H, m, H-9,10), 1.80 (2H, m, H-8), 3.40 (2H, dd, J = 9.63, 2.38, H-7), 3.58 (4H, m, H-2,6), 3.76 (2H, t, J = 10.41, H-12), 3.95 (2H, m, H-3), 4.07 (2H, d, J = 13.94, H-5), 7.40 (3H, m, H-4',3',5'), 7.58 (2H, d, J = 4.95, H-2',6').

^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm): 13.94 (C-11), 21.84 (C-10), 22.31 (C-8), 28.42 (C-9), 56.33 (C-3,5), 56.98 (C-7), 60.62 (C-2,6), 64.85 (C-12), 126.77 (C-1'), 129.42 (C-3',5'), 130.86 (C-4'), 133.40 (C-2',6').



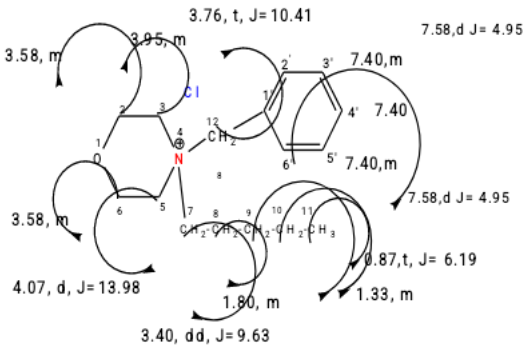
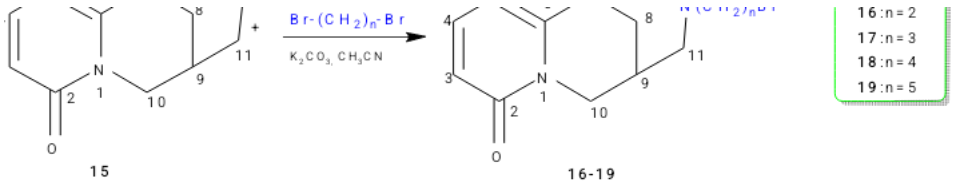


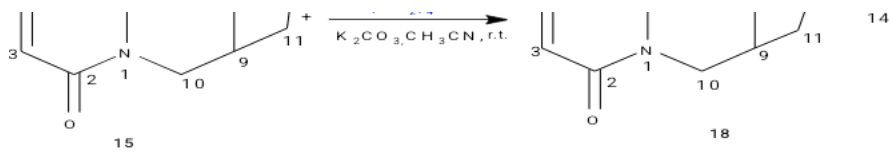
Figure 3. Crystal structures of compound 9

Reactions of the cytisine alkaloid with 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane. Cytisine contains a secondary amine (–NH–) group in its molecular structure. The nitrogen atom in this group acts as a nucleophilic center, which is why cytisine readily undergoes reactions with alkyl halides. The reaction of cytisine with dihaloalkanes proceeds via an SN2 mechanism, which is a one-step nucleophilic substitution process. In this mechanism, the bromide ion (Br^-) serves as a good leaving group. Initially, monoalkylation occurs, and subsequently, depending on the reaction conditions and the chain length of the dihaloalkane, intramolecular cyclization or the formation of quaternary ammonium salts may take place. Reactions of cytisine with 1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane were investigated. Among these experiments, only in the reaction with
1,4-dibromobutane did an intramolecular cyclization occur in a single step, leading to the formation of a quaternary ammonium salt.



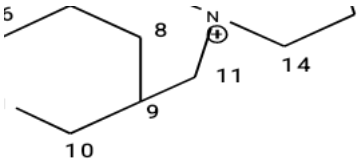
Scheme 3. General form of the reaction equation of cytisine with dibromoalkanes

In this context, N-(2-bromoethyl)cytisine (16), N-(3-bromopropyl)cytisine (17), N-(1,4-butylene) quaternary cytisine bromide (18), and N-(5-bromopentyl)cytisine (19) were considered. According to theoretical considerations, reactions of cytisine with all four dibromoalkanes were expected to predominantly yield tertiary amine derivatives, as illustrated in the general reaction scheme above. However, experimental results demonstrated that in the case of 1,4-dibromobutane, the reaction proceeded differently, leading to the formation of a quaternary cytisine salt in high yield.



Scheme 4. Reaction equation of cytisine with 1,4-dibromobutane

The molecular and crystal structure of N-(1,4-butylene) quaternary cytisine bromide was determined by single-crystal X-ray diffraction analysis. The obtained results confirm that the compound possesses a spatial arrangement characteristic of quaternary ammonium salts. According to the X-ray structural analysis, the cytisine framework retains its classical three-dimensional conformation. The carbonyl (C=O) group is oriented close to a planar arrangement, and the bond lengths between the carbonyl carbon and adjacent atoms correspond to typical values. This indicates that the cytisine core does not undergo structural distortion during the alkylation process. The nitrogen atom acts as a quaternary ammonium center, being bonded to both the cytisine moiety and the 1,4-butylene fragment. The geometry around the nitrogen atom is close to tetrahedral, which is consistent with its positively charged state. X-ray data show that the 1,4-butylene fragment adopts an extended zig-zag (anti) conformation. The $-CH_2-CH_2-CH_2-CH_2-$ chain is oriented outward relative to the cytisine core, thereby minimizing steric hindrance. This arrangement reduces internal strain within the molecule and contributes to its thermodynamic stability. In the crystal structure, the Br^- anion is located in close proximity to the quaternary ammonium cation, indicating strong electrostatic interactions. The bromide anion is situated near the nitrogen center, thereby enhancing the stability of the crystal lattice. In addition, several weak intermolecular interactions are observed in the crystal structure, including $N^+-H\cdots Br^-$ type ion–hydrogen bonds and $C-H\cdots Br^-$ secondary interactions. These interactions ensure an ordered packing of molecules within the crystal lattice, forming a dense three-dimensional structure. The crystal packing is characterized by an alternating arrangement of cations and anions, where the regular alternation of positive and negative charges contributes to the overall electrostatic stability. No aromatic π–π stacking interactions are observed between cytisine units, which can be explained by the bulky and non-planar nature of the molecular framework. The X-ray structural analysis unambiguously confirms the following: the cytisine framework remains intact during alkylation; the nitrogen atom participates as a quaternary ammonium center; the 1,4-butylene fragment adopts an extended conformation; bromide acts as a counterion forming an ion pair with the cation; the crystal structure is stabilized by ion–hydrogen bonding interactions. On this basis, the structure of the synthesized compound was reliably confirmed as N-(1,4-butylene) quaternary cytisine bromide by single-crystal X-ray diffraction analysis.



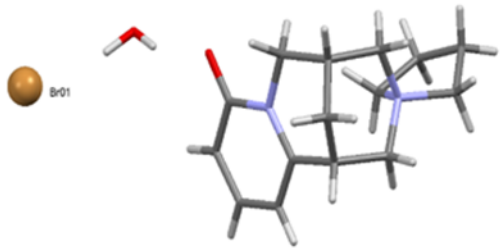


Table 6

Yields of products obtained from synthesized cytisine derivatives in the reactions (cytisine : dibromoalkane : K_2CO_3 : CH_3CN)

№	Obtained product	Molar ratio of reagents	Time (h)	Rf value	Product yield (%)
16	N-(2-brometil)sitizin	1:1,5	6	0,65	96
17	N-(3-brompropil)sitizin	1:1,5	5	0,68	63
18	Sitizinning to‘rtlamchi ammoniy tuzi	1:1,5	4	0,25	95
19	N-(5-brompentan)sitizin	1:1,5	7	0,83	61

The reactions were carried out at different molar ratios of the starting materials, namely 1:1, 1:1.1, 1:1.2, and 1:1.5, under reflux conditions in acetonitrile at its boiling temperature and for varying reaction times. Based on the data presented in the table, the optimal reaction conditions were identified as a molar ratio of 1:1.5 with a reaction duration of 4–7 hours. This behavior can be fully explained in terms of classical organic chemistry principles, including the thermodynamics of ring formation (Baeyer’s strain theory) and entropy effects. When cytisine reacts with 1,4-dibromobutane, after the initial alkylation step, the remaining bromoalkyl terminus undergoes intramolecular attack either by the second nucleophilic center of cytisine or by the same nitrogen atom, leading to the formation of a five-membered ring. Five-membered rings are thermodynamically the most favorable due to minimal ring strain; therefore, this reaction proceeds rapidly and smoothly, affording the corresponding product in high yield (95%). In the case of 1,2-dibromoethane, intramolecular cyclization would require the formation of a highly strained three-membered ring. As a result, the reaction proceeds exclusively through monoalkylation, leading to a stable intermediate that is also formed in high yield (96%). However, in the presence of 1,3-dibromopropane and 1,5-dibromopentane, the reaction pathway becomes significantly more complex. For the 1,3-dibromopropane system, cyclization would result in a strained four-membered ring, which is thermodynamically unfavorable. In the case of 1,5-dibromopentane, the carbon chain is excessively long and flexible. The conformational entropy barrier associated with intramolecular cyclization is therefore very high, as the reactive terminal must adopt a folded conformation within the same

molecule. These factors reduce the overall reaction rate and promote side reactions, including intermolecular coupling leading to oligomeric or polymeric by-products. Consequently, the yield of the target products decreases significantly to 61–63%.

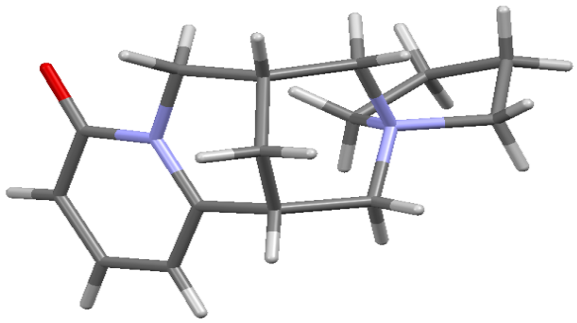


Figure 4. Crystal structure and structural formula of compound 20

On this basis, the structure of the synthesized compound was reliably confirmed as N-(1,4-butylene) quaternary cytisine bromide by single-crystal X-ray diffraction analysis. The third chapter of the dissertation, entitled **"Biological Properties of the Synthesized Compounds,"** presents the antibacterial and antifungal activities of the obtained compounds. The experimental studies were conducted in the 'Molecular Genetics' laboratories of the Institute of the Chemistry of Plant Substances under the supervision of the Head of the Laboratory, Sh.S. Azimova.

Antibacterial activity

According to the in vitro antimicrobial screening results carried out at the Molecular Genetics Laboratory of the Institute of Chemistry of Plant Substances, compounds 10, 12, and 21 exhibited antibacterial activity against various Gram-positive and Gram-negative bacterial strains. The observed biological activity of these compounds is related to the structural features of the bacterial cell wall as well as membrane permeability. Gram-positive bacteria possess a thick peptidoglycan (murein) layer, which determines their level of sensitivity to compounds **10, 11**, and **19**. Among the tested strains, *Bacillus subtilis* exhibited higher sensitivity compared to *Staphylococcus aureus*, with inhibition zone diameters of 18 mm, 16 mm, and 12 mm, respectively.

Table 7.

Antibacterial activity of 4-benzyl-4-nonylmorpholinium chloride (10), 4-benzyl-4-allylmorpholinium chloride (12), and N-(2-bromopentyl)cytisine (21) (antibacterial and antifungal activity tests)

Products	Diameter of inhibition zones (mm)				
	Gram-positive bacteria		Gram-negative bacteria		Fungi
	Bacillus	Staphylococcus	Escherichia coli	Pseudomonas	Candida albicans

	subtilis	aureus		aeruginosa	
4-Benzyl-4-nonylmorpholinium chloride (10)	18	8	6	6	N/A
4-Benzyl-4-allylmorpholinium chloride (11)	16	10	6	11	15
N-(5-Bromopentyl)cytisine (19)	12	6	6	7	N/A
Ampicillin/ Sulbactam (10μg+10μg/disc)	24	20	-	-	-
Gentamicin (10 μg/disc)	-	-	19	22	-
Fluconazole (25 μg/disc)	-	-	-	-	26

- No inhibition – N/A
- Weak activity – ≤ 6 mm
- Moderate activity – 8–14 mm
- Pronounced activity – 14–20 mm
- Strong activity – ≥ 20 mm

This indicates that compounds **10, 11**, and **19** have a more pronounced effect on the membrane structure of *B. subtilis*. Gram-negative bacteria are protected by an additional outer membrane, which makes them more resistant to antibiotics and other chemical agents. However, against *Escherichia coli*, all tested compounds showed antibacterial activity with an identical inhibition zone of 6 mm. In contrast, *Pseudomonas aeruginosa* demonstrated relatively lower sensitivity, with inhibition zones of 6 mm, 11 mm, and 7 mm, respectively. The fungus *Candida albicans* also exhibited sensitivity to compound 12, with an inhibition zone of 15 mm. This result indicates that compound 12 possesses antifungal activity in addition to its antibacterial properties.

The fourth chapter of the dissertation presents the experimental section, research methods, the synthesis of initial compounds, and the procedures for their various chemical modifications. Methods for the identification and structural elucidation of the compounds are described, including, in particular, chromatography (TLC), spectroscopy (IR, ^{1}H and ^{13}C NMR), and mass spectrometry results.

CONCLUSION

The reactions of morpholine with various alkyl halides, allyl and propargyl bromides were investigated, and the corresponding N-alkyl-, N-allyl-, and N-propargylmorpholines were synthesized. It was found that the product yield increases with the elongation of the alkyl chain in alkyl halides.

For the first time, the interaction of N-pentyl-, N-nonyl-, N-allyl-, and N-propargylmorpholines with benzyl chloride led to the synthesis of the corresponding 4-benzyl-4-alkylmorpholinium chlorides. The optimal

reaction conditions were studied, and analysis of the reactivity of alkyl and unsaturated substituents attached to the nitrogen atom showed that the reactivity of the N-alkyl derivatives decreases in the following order: N-allylmorpholine > N-pentylmorpholine ≈ N-nonylmorpholine > N-propargylmorpholine.

The reactions of cytisine with various dibromoalkanes (1,2-dibromoethane, 1,3-dibromopropane, 1,4-dibromobutane, and 1,5-dibromopentane) were studied. The results showed that the secondary nitrogen atom in the cytisine molecule acts as a nucleophilic center, leading to the formation of N-alkylated products. Depending on the reaction conditions and the length of the dibromoalkane chain, an intramolecular nucleophilic substitution occurs in the second stage, resulting in the formation of new cyclic derivatives. Based on the obtained results, an SN2 nucleophilic substitution mechanism was proposed.

Single crystals of the synthesized compounds, including 4-benzyl-4-pentylmorpholinium chloride, 4-benzyl-4-nonylmorpholinium chloride, and the cytisine derivative obtained with 1,4-dibromobutane, were grown and their structures were studied by X-ray crystallographic analysis. The obtained structural data were deposited in the Cambridge Crystallographic Data Centre (CCDC).

The synthesized compounds, namely 4-benzyl-4-nonylmorpholinium chloride, 4-benzyl-4-allylmorpholinium chloride, and N-(5-bromopentyl)cytisine, were found to exhibit bactericidal activity against Gram-positive bacteria (Bacillus subtilis, Staphylococcus aureus) and Gram -negative bacteria (Escherichia coli, Pseudomonas aeruginosa), as well as fungicidal activity against the pathogenic fungus Candida albicans.

ЯХШИЛИКОВА ЗАРИФА АБДИМАННОНОВНА

АЛКИЛИРОВАНИЕ ЦИТИЗИНА И МОРФОЛИНА И СИНТЕЗЫ НА ОСНОВЕ АЛКИЛНЫХ ПРОДУКТОВ

02.00.03 – Органическая химия

АВТОРЕФЕРАТ ДИССЕРТАЦИИ ДОКТОРА ФИЛОСОФИИ (PhD) ПО ХИМИЧЕСКАМ НАУКАМ

Ташкент – 2026

Тема диссертации доктора философии (PhD) зарегистрирована в высшей аттестационной комиссии при Министерстве высшего образования, науки и инноваций Узбекистана за номером B2024.2PhD/K761.

Диссертация выполнена в Национальном университете Узбекистана.

Автореферат диссертации на трех языках (узбекском, английском, русском (резюме)) размещен на веб-странице Ученого совета (ik-kimyo.nuu.uz) и на

Информационно-образовательном портале «ZiyoNet» (www.ziyonet.uz).

Научный руководитель:	**Холиков Турсунали Суюнович** доктор химических наук, профессор
Официальные оппоненты:	**Максумов Абдулхамид Гафурович** доктор химических наук, профессор **Матчанов Алимджон Давлетбаевич** доктор химических наук, профессор
Ведущая организация:	**Ташкентский фармацевтический институт**

Защита диссертации состоится на заседании Ученого совета под номером DSc.03/2025.27.12.K.01.13.M в Национальном университете Узбекистана ____ 2026 года в ____ часов. (Адрес: ул. Университетская 4, г. Ташкент).

С диссертацией можно ознакомиться в Центре информационных ресурсов Национального университета Узбекистана (зарегистрирован под номером___). (Адрес: г. Ташкент, ул. Университетская, 4).

Автореферат диссертации разослан «___» _____ 2026 года.

(Реестр за № от «__» _____ 2026 года).

М.А. Махкамов
Заместитель председателя
Научного совета по присуждению
учёных степеней, д.х.н профессор

У.О. Рузметов
Ученый секретарь
Научного совета по присуждению
учёных степеней, д.х.н профессор

А.К. Абдушукуров
Председатель научного семинара при
Научном совете по присуждению
учёных степеней, д.х.н профессор

ВВЕДЕНИЕ (Аннотация диссертации доктора философии (PhD))

Цель исследования. Цель исследования заключается в проведении синтезов на основе алкилирования цитизина и морфолина, а также их алкильных производных.

Объект исследования. В качестве объекта исследования выбраны цитизин и морфолин, алкилирующие реагенты, алкилпроизводные, а также четвертичные аммониевые соли.

Научная новизна исследования заключается в следующем:

В реакциях морфолина с монохалогеналканами установлено, что в ряду N-бутилморфолин <N-пентилморфолин <N-гексилморфолин
<N -нонилморфолин с увеличением числа метиленовых групп ($-CH_2-$) наблюдается повышение выхода продукта. Высокий выход реакции в этанольной среде при 78 °C, протекающей по механизму S_N2, объясняется влиянием природы растворителя и температурного режима на эффективность образования продукта.

Впервые синтезированы N-алкил- (N-аллил-, N-пропаргил-) морфолины в ацетонитрильной среде, а также четвертичные аммониевые соли, такие как 4-бензил-4-пентил-, 4-бензил-4-нонил-, 4-бензил-4-аллил- и 4-бензил-4-пропаргилморфолиний хлориды. Показано, что при мольном соотношении N-аллил- и N-пропаргилморфолинов с бензилхлоридом 1:1,2 достигается высокий выход реакции (96%).

В процессе алкилирования цитизина впервые осуществлён одностадийный синтез внутрикольчатого соединения — N-(1,4-бутилен)-четвертичного бромида цитизина, при котором с выходом 95% образуется стабильное циклическое соединение с орторомбической кристаллической структурой (α = β = γ = 90°).

На основе N-гексилморфолина в присутствии катализатора хлорида железа (III) синтезирован 4-гексил-4-нонилморфолиний бромид, что свидетельствует о возможном проявлении каталитических свойств кислоты Льюиса в данной реакции.

ИК-спектры N-алкил-, N-аллил- и N-пропаргилморфолинов подтверждают отсутствие характерных для морфолина валентных колебаний N–H в области 3300–3400 $см^{-1}$ и наличие полос поглощения алифатических C–H связей в области 2850–2960 $см^{-1}$, что свидетельствует об их принадлежности к третичным аминам. В спектрах ^1H ЯМР четко идентифицированы сигналы метиленовой группы, связанной с атомом азота (H-7), в области 2,20–2,35 м.д. Кристаллическая структура 4-бензил-4-нонилморфолиний хлорида установлена методом рентгеноструктурного анализа, который

подтвердил его кристаллизацию в моноклинной системе (a = 8,7990(5) Å, b = 7,4720(4) Å,
c = 32,998(2) Å, β = 95,561(3)°).

Внедрение результатов исследования

На основе синтеза новых четвертичных аммониевых солей, полученных на базе N-пентилморфолина, N-нонилморфолина и цитизина, а также их химической модификации, установлено следующее: кристаллические структуры трех соединений были определены и внесены в международную Кембриджскую кристаллографическую базу данных (The Cambridge Structural Database, https://www.ccdc.cam.ac.uk), где им присвоены идентификационные номера CCDC: 2277070, 2541862 и 2541863. Это позволило проводить сравнительное исследование синтезируемых аналогичных соединений и их пространственных структур.

Полученные результаты были использованы в рамках фундаментального проекта FL–7923051904 «Синтез наномасштабных катализаторов и их носителей для получения винильных соединений, их структура и электронные свойства» (2024–2025 гг.), выполняемого в Национальном университете Узбекистана (справка Агентства инновационного развития при Министерстве высшего образования, науки и инноваций Республики Узбекистан от 22 апреля 2026 года № 01-02/1/1677).

В результате были усовершенствованы методические подходы к синтезу новых соединений, определению их кристаллической структуры и физико-химических свойств. Полученные научные результаты также открывают возможности для применения в исследованиях, направленных на создание перспективных функциональных материалов и оценку их свойств.

Структура и объём диссертации. Структура диссертации включает введение, три главы, заключение, список использованной литературы и приложения. Объём диссертации составляет 110 страниц.

E’LON QILINGAN ISHLAR RO‘YXATI
СПИСОК ОПУБЛИКОВАННЫХ РАБОТ
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