O‘ZBEKISTON MILLIY UNIVERSITETI HUZURIDAGI
ILMIY DARAJALAR BERUVCHI
DSc.03/30.12.2019K.01.03 RAQAMLI ILMIY KENGASH
O‘ZBEKISTON MILLIY UNIVERSITETI

SALIYEVA GULRUX BAXODIROVNA

4,6-DIAMINO-2-MERKAPTOPIRIMIDIN ASOSIDA *S*-ALKIL MAHSULOTLARI SINTEZI VA ULARNING BIOLOGIK FAOLLIGI

02.00.03 – Organik kimyo

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

Toshkent – 2025

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Kimyo fanlari bo‘yicha falsafa doktori (PhD) dissertatsiyasi avtoreferati mudarijasi

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

Оглавление автореферата диссертации доктора философии (PhD) по химическим наукам

Kimyo fanlari bo'yicha falsafa doktori (PhD) dissertatsiyasi mavzusi O'zbekiston Respublikasi Oliy ta'lim, fan va innovatsiyalar vazirligi huzuridagi Oliy attestatsiya komissiyasida B2024.4PhD/K622 raqam bilan ro'yxatga olingan.

Dissertatsiya O'zbekiston Milliy universitetida bajarilgan.

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(2025-yil "21" 05 / 13 raqamli reyestr bayonnomasi).

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KIRISH (falsafa fanlari doktori (PhD) dissertatsiyasi annotatsiyasi)

Dissertatsiya mavzusining dolzarbligi va zarurati. Bugungi kunda dunyoda pirimidin hosilalari tibbiyotda va farmatsevtikada turli kasalliklarga qarshi dori vositalari, agrosanoatda gerbitsid va fungitsid sifatida keng miqyosida qo‘llaniladi. Ayniqsa, pirimidinning amino hosilalari saratonga qarshi ishlatilayotgan *gemcitabin*, *crizotinib*, *acalabrutinib* va *imatinib* kabi preparatlar ko‘rinishida ishlatiladi. Bu preparatlarning analoglarini yaratish, ularni olish usullarini takomillashtirish va amaliyotga qo‘llash muhim amaliy ahamiyat kasb etadi.

Jahonda DAMP asosida *S*-alkil va *S*-atsetoamid birikmalarini sintez qilishning samarali usullarini ishlab chiqish hamda ushbu reaksiyalar uchun yangi katalizatorlarni tavsiya etish yo‘nalishida keng ko‘lamli tadqiqotlar olib borilgan. Jumladan, DAMPning alifatik, aromatik va galogen tutgan geterohalqali birikmalar bilan alkillash reaksiyalari, shuningdek, monoxlorsirka kislota amidlari, metallokompleks birikmalar va nanokatalizatorlar ishtirokida amalga oshiriladigan reaksiyalar muhim ilmiy ahamiyatga ega.

Mamlakatimizda so‘nggi yillarda ta’lim va sanoatni rivojlantirishning uzviy bog‘liqligini ta’minlash, shuningdek, 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 iqtisodyot 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]. Bu borada aminomerkaptopirimidinning *S*-alkil hosilalari sintezining qulay usullarini topish va ularning tuzilishini zamonaviy fizik-kimyoviy usullar bilan tahlil qilish, jarayonlarga ta’sir etuvchi asosiy omillarni va reaksiya qonuniyatlarini aniqlash, olingan birikmalarning fizik-kimyoviy va biologik xossalarini aniqlash hamda tarkibida yangi farmakofor guruhlari bo‘lgan biologik faol moddalarni yaratishga yo‘naltirilgan ilmiy-amaliy tadqiqotlar muhim o‘rin tutadi.

O‘zbekiston Respublikasi Prezidentining 2021-yil 13-fevraldagi “Kimyo sanoati korxonalarini yanada isloh qilish va moliyaviy sog‘lomlashtirish, yuqori qo‘shilgan qiymatli kimyoviy mahsulotlar ishlab chiqarishni rivojlantirish chora-tadbirlari to‘g‘risida”gi PQ-4992-son qarori, 2020-yil 12-avgustdagi “Kimyo va biologiya yo‘nalishlarida uzluksiz ta’lim sifatini va ilm fan natijadorligini oshirish chora tadbirlari to‘g‘risi”gi PQ-4805-son qarori va 2022-yil 28-yanvardagi Yangi O‘zbekistonning 2022-2026-yillarga mo‘ljallangan taraqqiyot strategiyasi to‘g‘risidagi”gi PF-60-son farmoni hamda mazkur faoliyatga tegishli boshqa me’yoriy hujjatlarda belgilangan vazifalarni amalga oshirishda ushbu disseratatsiya ishi muayyan darajada xizmat qiladi.

[1] O‘zR Prezidentining 2022 yil 6-iyuldagi PF-60-son “2022-2026-yillarga mo‘ljallangan yangi O‘zbekistonning taraqiyyot strategiyasi to‘g‘risida”gi Farmoni”

Tadqiqotning respublika fan va texnologiyalari rivojlanishining ustuvor yo‘nalishlariga mosligi. Mazkur tadqiqot respublika fan hamda texnologiyalar rivojlanishining VII. Kimyo texnologiyalari va nanotexnologiyalar ustuvor yo‘nalishlariga muvofiq bajarilgan.

Muammoning o‘rganilganlik darajasi. Dunyoning ko‘plab rivojlangan davlatlarida 2-merkaptopirimidin asosida *S*-alkil mahsulotlari sintezi va ularning biologik faolligi asosidagi izlanishlar jadal olib borilmoqda. Xususan, xorijlik olimlar M.A.Yusuf amino-2-merkaptopirimidin asosidagi *S*-alkil hosilalarining antibakterial va fungitsidlik xususiyatlarini o‘rgangan. Yangi biologik faol moddalarning sintezi va ularning mikroorganizmlar hamda zamburug‘larga qarshi samaradorligini tahlil qilgan. R.K.M.Mahmoud *S*-alkil 6-amino-2-merkaptopirimidin sintezi va uning antibakterial xususiyatlarini o‘rgangan. Bu moddalarning mikroorganizmlarga (bakteriyalar, viruslar) fungitsidlik ta’sirini tahlil qilgan. Xiu Zhang, A.Tariq, M.George, N.Mikhail, M.Abdullahi, M.Hassan, B.Luislar yangi dori moddalarini yaratish uchun sintez jarayonlarini optimallashtirish, *S*-alkil birikmalarining rak va virusga qarshi ta’sirini, shuningdek, ularning toksikologik tahlillarini o‘rgangan.

Respublikamizda bu yo‘nalishdagi ishlarning rivojiga O‘zbekiston olimlari tomonidan tabiiy va sintetik pirimidinlar bo‘yicha katta hajmdagi tadqiqotlar olib borilgan. Bunga misol qilib, akademik S.Yu.Yunusov va hamkasblari, professorlar X.M.Shahidoyatov, N.D.Abdullayev, B.J.Elmurodov, V.I.Vinogradova, X.U.Xodjaniyozov, X.A.Bozorov va boshqalar o‘simliklardan pirimidin hosilalarini ajratib olib, bu birikmalarning umumiy sintezi va kimyoviy xossalari bo‘yicha ilmiy tadqiqotlar olib borganlar.

Adabiyotlar tahlilining ko‘rsatishicha, aminomerkaptopirimidinlarning *S*-alkil mahsulotlar sintezi bo‘yicha keng qamrovli tajriba natijalari bo‘lishiga qaramasdan, ularning *S*-allil (propargil), *S*-alkilatsetoefir hosilalari sintezi o‘rganilmagan. Shu sababli, merkaptopirimidinning alkil galogenidlar bilan reaksiyalarini o‘rganish va sintez qilingan birikmalarning biologik faolligini aniqlash alohida ilmiy qiziqish kasb etadi.

Dissertatsiya mavzusining dissertatsiya bajarilgan oliy ta’lim muassasasi ilmiy tadqiqot ishlari rejalari bilan bog‘liqligi. Dissertatsiya O‘zbekiston Milliy universitetining OT-F-7-52 (OT-F-7-50, OT-F-7-56, OT-F-7-58) “Turli tabiatli organik hamda noorganik moddalarning ta’sirlashish qonuniyatlari va reaksion qobiliyati hamda berilgan kompleks xossali yangi birikmalar olish” (2017-2020-yy.) va AM-FZ-2019081452 “Etilen asosida siklogeksan sintezi texnologiyasini ishlab chiqish” (2020-2022-yy.) mavzularidagi ilmiy tadqiqot loyihasining fundamental loyihalari doirasida bajarilgan. `

Tadqiqotning maqsadi. 4,6-Diamino-2-merkaptopirimidin asosida *S*-alkil mahsulotlari sintezi va ularning biologik faolligini tadqiq qilishdan iboratdir.

Tadqiqotning vazifalari:

4,6-diamino-2-merkaptopirimidinni (DAMP) turli sharoitlarda yangi *S*-alkil hosilalarini sintez qilish;

DAMPni to‘yinmagan allil (propargil) bromid bilan proton va aproton erituvchilar ishtirokida *S*-allillash (propargillash) reaksiyalarini olib borish;

DAMPni almashingan benzil galogenidlar bilan *S*-benzillash reaksiyalarida reaksion qobiliyatini aniqlash;

Alkil galogenidlarning DAMP bilan *S*-alkillash reaksiyalaridagi nisbiy faollik qatorini aniqlashda, reaksiya borishiga harorat, reaksiya davomiyligi, erituvchilar tabiati, dastlabki moddalar nisbati ta’sirini o‘rganish;

DAMPning yangi tioalkilatsetoefir hosilalarini muqobil usulda sintez qilish;

sintez qilingan moddalarning tuzilishini zamonaviy fizik-kimyoviy tadqiqot usullari yordamida isbotlash;

sintez qilingan birikmalarning biologik faolligini aniqlash.

Tadqiqotning obyekti 4,6-diamino-2-merkaptopirimidin (DAMP), DAMPning *S*-natriyli tuzi, *n*-butil-, *n*-pentil-, *n*-geksil-, *n*-geptil-, *n*-nonil-, allil-, propargil-, benzil-, 4-metilbenzil-, 2,4-dimetilbenzil-, 2,5-dimetilbenzil-, 2,6-dimetilbenzil-, 3-xlorobenzil-, 4-xlorobenzil-, 2,4-dixlorobenzil-, 2,6-diftorobenzil-alkiltio hosilalari. DAMPning metil-, etil-, allil-, propargil-, benzil-, 2,4-dimetilbenzil-, 2,5-dimetilbenzil-2-tioalkilatsetoefir hosilalari tadqiqot obyektlari hisoblanadi.

Tadqiqotning predmeti. DAMPning oltingugurt atomida nukleofil almashinish reaksiyalari, *S*-alkil, *S*-to‘yinmagan alkil, S-benzil va *S*-alkilatsetoefir reaksiya mahsulotlarining fizik-kimyoviy hamda biologik xossalarini aniqlash hisoblanadi.

Tadqiqot usullari. Zamonaviy organik kimyo usullari, spektrometrik (Yuqori samarali xromotomass (YuSMS), suyuqlik xromotomas (SXMS)), spektroskopik (YaMR, IQ, rentgen tuzilish tahlili (RTT), yupqa qatlam xromatografiya (YuQX) va biologik tadqiqot usullari qo‘llanilgan.

Tadqiqotning ilmiy yangiligi quyidagilardan iborat:

Ilk bor DAMP ning *n*-geptil, *n*-nonil, allil-, propargil-, 4-metilbenzil-, 2,4-dimetilbenzil-, 2,5-dimetilbenzil-, 2,6-dimetilbenzil-, 3-xlorobenzil-, 4-xlorobenzil-, 2,4-dixlorobenzil-, 2,6-diftorobenzil- hosilalari sintez qilingan;

Ilk bor “*one pot”* sintez usulida DAMPning allil-, propargil-, benzil-, 2,4-dimetilbenzil-, 2,5-dimetilbenzil- radikal tutgan tioalkilatsetoefir birikmalari tadqiq etilgan;

S-alkil hosilalarida zanjir uzunligi ortishi bilan reaksiya unumi kamaygan, harorat 20-70 ^{o}C gacha ortganda reaksiya unumi ortib borib, *n*-butil, *n*-pentil, *n*-geksil hosilalar uchun harorat 50 ^{o}C da, *n*-geptil, *n*-nonil hosilalar uchun esa 70 ^{o}C da monomahsulot hosil bo‘lishi aniqlangan;

DAMPning allil-, propargil- hosilalari sintezi proton va aproton erituvchilarda olib borilganda reaksiya unumi aproton erituvchilarda yuqori bo‘lgan. DAMPning natriyli tuzi bilan allil, propargil bromidlar nisbati 1:2 bo‘lganda reaksiya tezligi va reaksiya unumi yuqoriligi (90 %) isbotlangan;

DAMP bilan elektronodonor o‘rinbosarlar saqlagan dimetilalmashgan benzil hosilalarning nukleofil almashinish reaksiyalariga kirishish qobiliyati 2,4-

dimetilbenzil xlorid < 2,5-dimetilbenzil xlorid < 2,6-dimetilbenzil xlorid qatorda kamayib borishi aniqlangan;

DAMP asosida olingan *S*-alkil hosilalarning tuzilishi mass spektrometrik, YaMR, IQ-spektroskopik va RTT usullari yordamida isbotlangan;

Etalon “sisplatin” (11,07 μM), dori vositasiga nisbatan DAMP ning 2,5-dimetilbenzil hosilasi (4,42 μM) bachadon bo‘yni saraton hujayralariga (Hela) 2.5 marta ko‘proq foallik ko‘rsatib, tirik hujayralarning 95,8 %ni nobud qilgan.

Tadqiqotning amaliy natijalari quyidagilardan iborat:

DAMP asosida *S*-alkillash reaksiyalarning maqbul sintez usullari topilgan;

ilk bor DAMPning allil, propargil bromidlar bilan alkillash reaksiyalarida mono mahsulot olish usullari tavsiya etilgan;

birinchi marta DAMPning S-alkilatsetoefir hosilalari sintezining maqbul usullari ishlab chiqilgan;

ilk bor 2-{(2,4-dimetilbenzil)tio}pirimidin-4,6-diaminning fazoviy tuzilishlari hamda barcha kristallografik kattaliklari isbotlangan va Xalqaro Kembrij kristallografik ma’lumotlar bazasiga kiritilgan.

Tadqiqot natijalarining ishonchliligi. Qo‘llanilgan xromatografik, fizik-kimyoviy usullar IQ-, ^{1}H, ^{13}C, HMBC, HSQC, COSY, YAMR-spektroskopiya, YuSMS, SXMS, YuSSX, YuQX, rentgen tuzilish tahlili (RTT) va biologik usullar ma’lumotlari asosida tasdiqlangan, shuningdek, tadqiqot natijalarining ishonchliligi qator xalqaro ilmiy jurnallarda chop etilganligi bilan asoslanadi.

Tadqiqot natijalarining ilmiy va amaliy ahamiyati. Tadqiqot natijalarining ilmiy ahamiyati shundan iboratki, DAMPni selektiv *S*-alkillash ishqoriy sharoitda alkil galogenidlar, to‘yinmagan alkil galogenidlar, almashingan benzil galogenidlar va monoxlorsirka kislota bilan *S*-alkil, *S*-almashingan benzil, *S*-alkilatsetoefir hosilalari sintez qilingan, turli sharoitlarda nukleofil almashinish reaksiyalari bo‘yicha tizimli tadqiqotlar o‘tkazilgan, reaksiyalar yo‘nalishiga ta’sir qiluvchi asosiy omillar aniqlanganligi bilan izohlanadi.

Tadqiqot natijalarining amaliy ahamiyati shundan iboratki, sintez qilingan birikmalar orasida yuqori sitotoksik faollikni namoyon qiluvchi *S*-alkil birikmalar borligi aniqlangan va ularni maqbul sintez usullari ishlab chiqilgan. Umumiy 23 ta modda sintez qilingan shulardan 17 tasi yangi modda, sintez qilingan moddalar orasida biologik foal moddalar borligi isbotlangan. Sintez qilingan 2-{(2,4-dimetilbenzil)tio}pirimidin-4,6-diaminning rentgen tuzilish tahlili usullari yordamida yangi ekanligi va kristall tuzilishi isbotlanganligi hamda xalqaro Kembridj Markaziy kristallografik ma’lumotlar bazasiga kiritilganligi bilan belgilanadi.

Tadqiqot natijalarining joriy qilinishi. DAMPning alkil galogenidlar bilan reaksiyalari bo‘yicha olingan ilmiy natijalar asosida:

2-{(2,4-dimetilbenzil)tio}pirimidin-4,6-diaminning rentgen tuzilish tahlili (RTT) natijalari Kembridj kristallografik markazi ma’lumotlar bazasiga kiritilgan (Cambridge Crystallographic Data Centre ning 2025-yil 25-martdagi 2431935-

sonli ma’lumotnoma). Natijada, almashingan tiopirimidin hosilalari tarkibiga kiruvchi yangi moddalarning tuzilishini aniqlash imkonini bergan;

Toshkent farmatsevtika instituti “Innovatsion farmatsevtik birikmalar” ilmiy laboratoriyasida bajarilgan “Akvaporin kanallarini biologik faol birikmalar yordamida bloklash orqali saraton hujayralari proliferatsiyasini cheklash: molekulyar darajadagi eskperimental tadqiqotlar” (2022-2024-yy.) mavzusida bajarilgan fundamental loyihada foydalanilgan (Oliy ta’lim, fan va innovatsiyalar vazirligi 2025-yil 14-mart № 03/17-668-son ma’lumotnomasi). Natijada, 4,6-diamino-2-merkaptopirimidin asosida sintez qilingan *S*-alkil birikmalar jigar saraton (HepG2) hujayrasini ingibirlash faolligini namoyon qilgan.

Tadqiqot natijalarining aprobatsiyasi. Mazkur tadqiqot natijalari bo‘yicha 4 ta, shu jumladan, 2 ta xalqaro va 2 ta respublika ilmiy-amaliy anjumanlarida ma’ruza qilingan hamda muhokamadan o‘tkazilgan.

Tadqiqot natijalarining e’lon qilinishi. Dissertatsiya ishi bo‘yicha jami 9 ta ilmiy ishlar nashr qilinib, ulardan O‘zbekiston Respublikasi Oliy attestatsiya komissiyasining doktorlik dissertatsiyalari asosiy ilmiy natijalarini chop etish tavsiya etilgan ilmiy nashrlarda 5 ta maqola, ulardan 2 ta respublika va 3 ta xorijiy jurnallarda nashr etilgan.

Dissertatsiyaning tuzilishi va hajmi. Dissertatsiya tarkibi kirish, 4 ta bob, xulosalar, foydalanilgan adabiyotlar ro‘yxati va ilovalardan iborat. Dissertatsiyaning hajmi 120 betni tashkil qiladi[1].

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 “**Almashingan pirimidinlar sintezi, xossalari va qo‘llanilish sohalari**” deb nomlangan **birinchi bobida** adabiyotlar tahlili keltirilgan bo‘lib, unda bir qator pirimidin hosilalari to‘g‘risidagi ma’lumotlar tahlil qilingan, ularning sintezi, modifikatsiyasi, biologik faolligiga doir adabiyotlarning hozirgi holati tahlil qilingan.

Dissertatsiyaning “**4,6-Diamino-2-merkaptopirimidin asosida *S*-alkil hosilalari sintezi (Olingan natijalarning muhokamasi)**” deb nomlangan **ikkinchi bobida** DAMP asosida turli sharoitlarda *S*-alkillash, *S*-allillash(propargillash), *S*-benzillash va *S*-alkilatsetoefir olish reaksiyalari amalga oshirilgan. Reaksiya natijasida hosil bo‘lgan birikmalarning kimyoviy tuzilishini tahlili xromotografiya, spektroskopiya (IQ, ^{1}H, ^{13}C HSQC va HMBC YaMR), hamda yuqori samarali mass spektrometriya va RTT natijalari keltirilgan.

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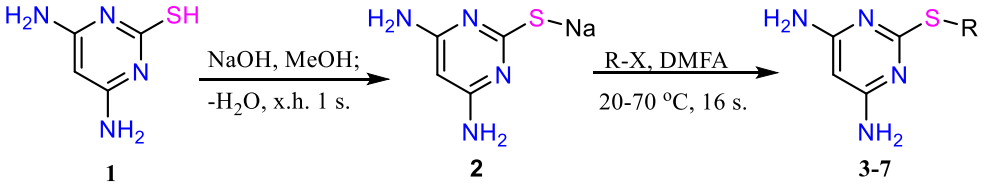
[1] *Muallif O‘zR FA Bioorganik kimyo instituti professori A.D.Matchanovga dissertatsiya ishini bajarishda ko‘rsatgan yordamlari uchun o‘zining samimiy minnatdorchiligini bildiradi.*

DAMPning alkil galogenidlar bilan reaksiyada, unumga haroratning ta’siri o‘rganildi. Dastlabki reagentlarning mol nisbatlari 1:1,2 bo‘lib, birinchi bosqichda erituvchi sifatida MeOH, ikkinchi bosqichda esa DMFA ishlatilib, reaksiya 16 soat davomida olib borildi. Olingan natijalar quyidagi 1-jadvalda keltirilgan.



1 **2** **3-7**

Bu yerda R=C_4H_9 (**3**); C_5H_{11} (**4**); C_6H_{13} (**5**); C_7H_{15} (**6**); C_9H_{19} (**7**).

1-jadval.

4,6-Diamino-2-merkaptopirimidinni alkil galogenidlar bilan reaksiyalari unumiga harorat va reagentlar nisbati (DAMP:NaOH:alkil galogenid (1:2,5:1,2) ta’siri

№	Reagentlar	Mahsulot unumi (%) va harorat					Erituvchi
		20 °C	**40° C**	**50° C**	**60°C**	**70°C**	DMFA
3	DAMP, NaOH, *n*-Butil bromid	60	66	70	-		DMFA
4	DAMP, NaOH, *n*-pentil bromid	58	62	68	-	-	DMFA
5	DAMP, NaOH, *n*-geksil bromid	55	59	64	-	-	DMFA
6	DAMP, NaOH, *n*-geptil bromid	52	57	62	68	74	DMFA
7	DAMP, NaOH, *n*-nonil bromid	40	45	51	63	71	DMFA

Ushbu jadvaldan ko‘rinadiki, 20 °C da alkil zanjiri uzayishi bilan reaksiyaga kirish faolligi quyidagi qatorda kamayib boradi.

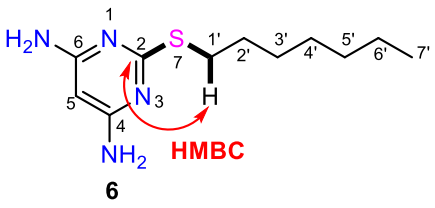
***n*-C_4H_9-< *n*-C_5H_{11}-< *n*-C_6H_{13}-< *n*-C_7H_{15}-< *n*-C_9H_{19}-**

Buning sababini quyidagicha izohlash mumkin: Alkil guruhlari kuchli elektronoakseptor bo‘lmasa ham zanjir uzunligi ortishi bilan kichik induktiv ta’sir farqi yuzaga keladi, bu esa galogen bilan bog‘langan uglerodining elektrofilligini biroz pasaytiradi. Biroq bu ta’sir fazoviy to‘siqlarga nisbatan kamroq seziladi. Zanjir uzunligi oshgani sari masalan: *n*-C_4H_9-< *n*-C_5H_{11}-< *n*-C_6H_{13}-< *n*-C_7H_{15}-< *n*-C_9H_{19}- elektrofil uglerod atrofidagi hajmiy to‘siqlar kuchayadi. Bu nukleofilning uglerodga hujumini qiyinlashtiradi va reaksiyani sekinlashtiradi. Uzunroq alkil zanjirli birikmalar gidrofob xususiyatga ega bo‘lib, ular qutbli erituvchilarda (masalan, DMFA yoki DMSO) yomon eriydi.

Natijalardan ko‘rinadiki, DAMP alkil galogenidlar bilan 1:1,2 mol nisbatda metanol va DMFA erituvchisida qizdirilganda SH guruhi hisobiga *S*-alkil mahsulotlari – tioefirlar hosil bo‘ldi.

Sintez qilingan birikmalarning individualligi yupqa qatlam xromatografiyasi (YuQX) usuli yordamida aniqlangan. YuQX uchun metanol:xloroform (1:5) sistemasi tanlandi va sintez qilingan birikmalarning R_f qiymatlari aniqlangan.

Monoalkillash jarayonida uchta mahsulot hosil bo‘lishi mumkin (**6**, **8** va **9**,).



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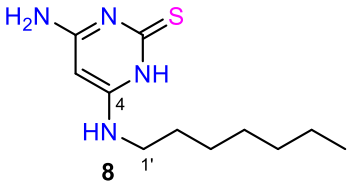

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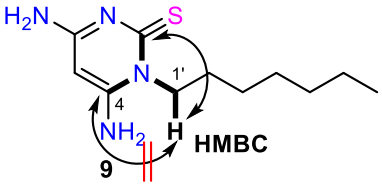


9

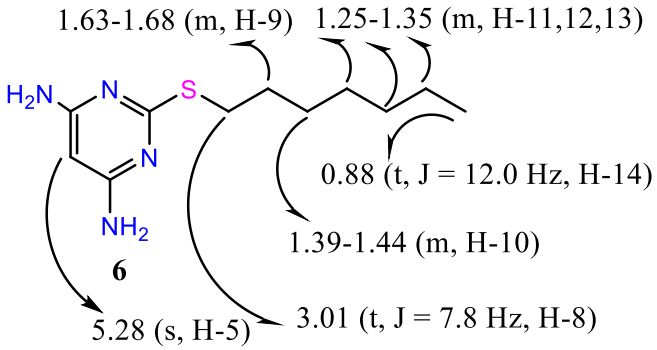
Shuning uchun mahsulotlar (**3-7**) tuzilishi keng qamrovli spektroskopik tahlillar yordamida aniqlik bilan o‘rganildi.

2-jadval.

4,6-Diamino-2-merkaptopirimidin bilan alkilgalogenidlarning reaksiyasidan olingan mahsulotlarning unumi va fizik-kimyoviy kattaliklari

Olingan mahsulot	Reagentlarning mol nisbati	Mahsulot unumi %	R_f qiymati	T_{suyuq} °C
3	1:1,2	70	0,62	91-92
4	1:1,2	68	0,62	92-93
5	1:1,2	64	0,62	80-81
6	1:1,2	**74**	0,62	-
7	1:1,2	71	0,62	-

6-Birikmaning ^{1}H YaMR spektrida geptil zanjirining terminal metil guruhi (H7') uchun δ 0.87 m.u. da triplet signal kuzatildi. n-Geptil guruhiga mansub o‘n to‘rtta metilen protonidan o‘ntasi (H2'–H6') δ 1.22–1.32, 1.36–1.41 va 1.60–1.65 m.u. oraliqda signallar berdi. Oltingugurt atomiga yaqin joylashgan ikkita metilen protoni (H1') esa δ 3.01 m.u. da triplet shaklida ko‘rindi. δ 5.26 m.u. dagi singlet signal esa pirimidin halqasidagi aromatik proton (H5) ga mos keldi.



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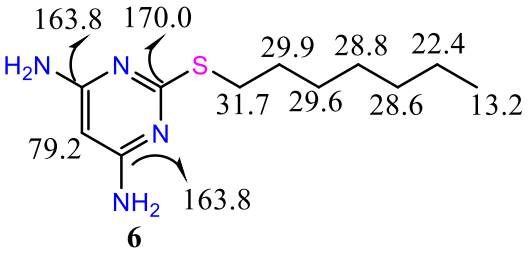
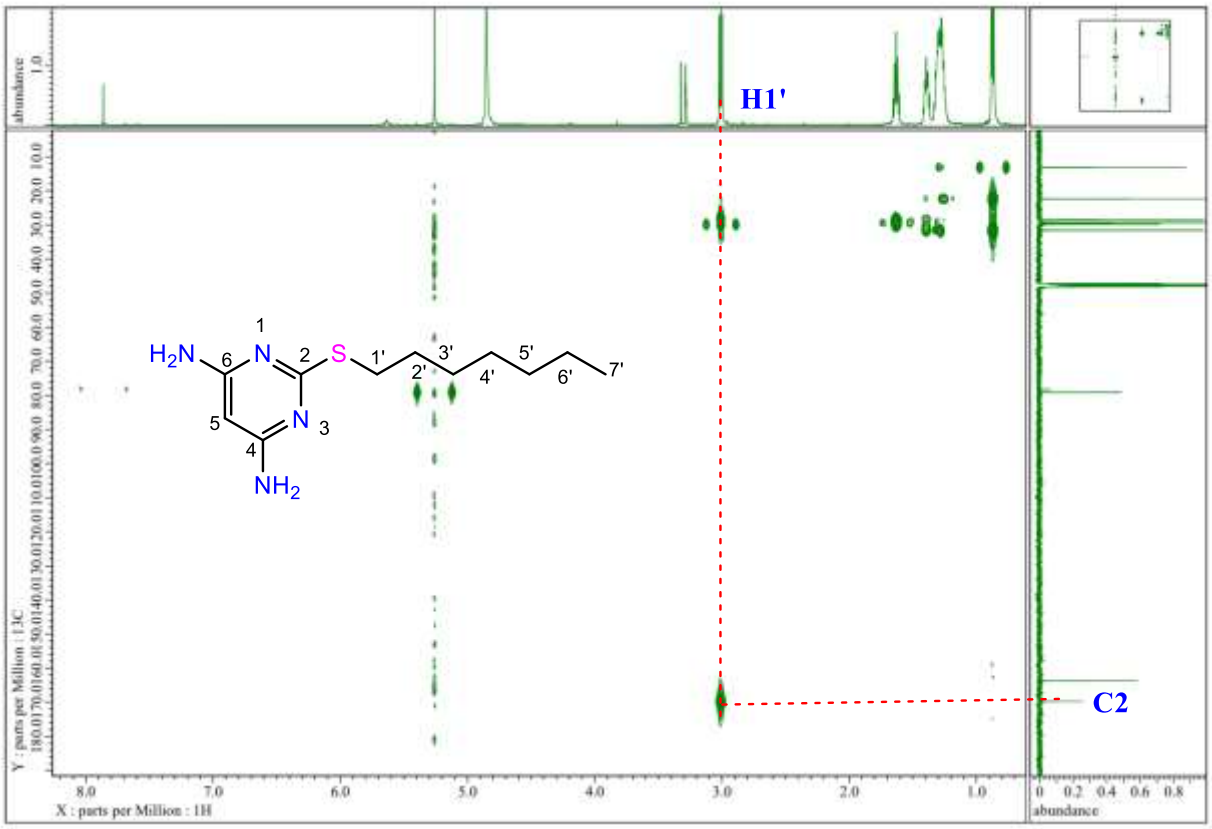


6

6-Birikmaning ^{1}H va ^{13}C YaMR spektr tahlili.

^{13}C YaMR spektrida terminal metil uglerod C7' δ 13.2 m.u. da kuzatildi, metilen uglerodlari C2'–C6' esa δ 22.4–29.9 m.u. oraliqda signal berdi, bu alifatik guruhga mos keldi. Oltingugurt atomiga tutash joylashgan C1' uglerodining kimyoviy siljishi δ 31.7 m.u. da signal berdi, bu esa *S*-alkillanishga xos bo‘lgan qiymatdir. Agar *N*-alkillangan mahsulot hosil bo‘lgan bo‘lsa, adabiyotlarga ko‘ra N-CH_2 signali taxminan δ 43 m.u. da signal bo‘lishi kerak edi. Aromatik uglerodlar δ 79.2 m.u. (C5), δ 163.8 m.u. (C4, C6), δ 170.0 m.u. da (C2) kimyoviy siljishlari aniqlandi.



1-rasm. 6-Birikmaning HMBC YaMR spektri tahlili.

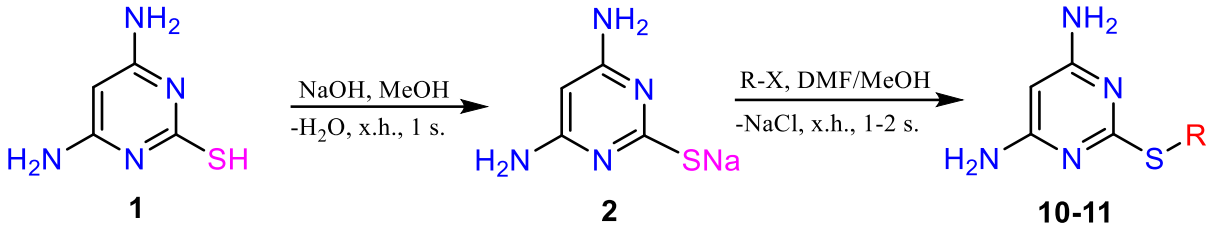
HMBC tahlili orqali alkillanish joyini aniq belgilashga e'tibor qaratildi. HMBC diagrammasini sinchkovlik bilan tahlil qilish natijasida muhim o'zaro ta'sir signallari aniqlangan bo'lib, aynan H1' va C2 o'rtasidagi eng muhim ^{4}JCH o'zaro ta'siri kuzatildi. Bu esa alkil guruhining oltingugurt atomi bilan bog'langanligini tasdiqlab, **6** birikmaning tuzilishiga mos kelishini ko'rsatdi. Yuqorida keltirilgan spektroskopik tahlillar natijasida **6** moddaning tuzilishi ishonchli tasdiqlandi. HMBC spektrida H1' va C2 o'rtasida muhim korrelyatsiya kuzatildi (**6**-birikma). Aksincha, hosil bo'lishi mumkin bo'lgan *N*-alkillangan mahsulotlar (**8** va **9**) hosil bo'lishi uchun HMBC spektrida H1' va C4 o'rtasida korrelyatsiya bo'lishi kerak edi. Biroq HMBC analizida bunday signal aniqlanmadi. Garchi organik birikmalarning YaMR orqali tuzilishini aniqlashda kuzatilmaslik ijobiy dalil bo'la olmasligini bilsak ham, biz ushbu bilvosita faktni yaxshiroq taxmin qilishimiz uchun ishlatdik (1-rasm).

Ushbu selektivlik "qattiq va yumshoq kislota va asos" (YuQKA) nazaryasi bo'yicha tushuntirish mumkin. Unga ko'ra, yumshoq asoslar (masalan, oltingugurt anionlari) yumshoq kislotalar (masalan, alkil galogenidlar) bilan reaksiyaga kirishishga moyildir.

4,6-Diamino-2-merkaptopirimidinning allil va propargil bromidlar bilan alkillash reaksiyasi

DAMP va to'yinmagan alkil galogenidlar asosida *S*-alkil hosilalar sintezi o'rganildi. Tadqiqot natijalariga ko'ra, DAMPning to'yinmagan alkil galogenidlar bilan reaksiyalari aproton erituvchilarda ishqoriy sharoitda olib borilganda reaksiya

tezligi va hosil bo‘layotgan mahsulotlarning unumdorligi sezilarli darajada oshishi kuzatildi.



Bu yerda: R = allil (**10**), propargil (**11**).

Ushbu jarayonni o‘rganish maqsadida DAMP va to‘yinmagan alkil bromidlar o‘rtasida *S*-alkillash reaksiyalari amalga oshirildi. Dastlab, DAMP va NaOH metanolda eritildi, magnitli aralashtirgich yordamida 1 soat davomida aralashtirildi. Ushbu bosqichda DAMP ning Na li tuzi hosil bo‘ldi, so‘ngra metanol rotorli bug‘latgich yordamida butunlay haydab olindi.

3-jadval.

4,6-Diamino-2-merkaptopirimidinning allil, propargil bromidlar bilan reaksiyalariga erituvchi, reaksiya davomiyligi va dastlabki reagentlarning nisbati reaksiya unumiga ta’siri

№	Erituvchi	nisbat	vaqt	unum	nisbat	vaqt	unum	nisbat	vaqt	unum
10	MeOH	1:1	2	58	1:1,2	1,5	59	1:2	1	62
	DMFA	1:1	2	86	1:1,2	1,5	87	1:2	1	89
11	MeOH	1:1	2	56	1:1,2	1,5	59	1:2	1	62
	DMFA	1:1	2	85	1:1,2	1,5	87	1:2	1	90

Keyingi bosqichda hosil bo‘lgan DAMP ning Na li tuzi DMFAda eritildi. So‘ngra, allil (propargil) bromid tomchilatib qo‘shilib, aralashma magnitli aralashtirgichda 1-2 soat davomida reaksiya olib borildi. Reaksiya natijasida *S*-alkil hosilalarining hosil bo‘lishi qayd etildi.

DAMP ning to‘yinmagan allil (propargil) bromidlar bilan reaksiyalari uchun eng qulay sharoit ishqoriy muhit bo‘lib, DMFA kabi aproton erituvchilardan foydalanish orqali reaksiya unumini oshirish mumkin.

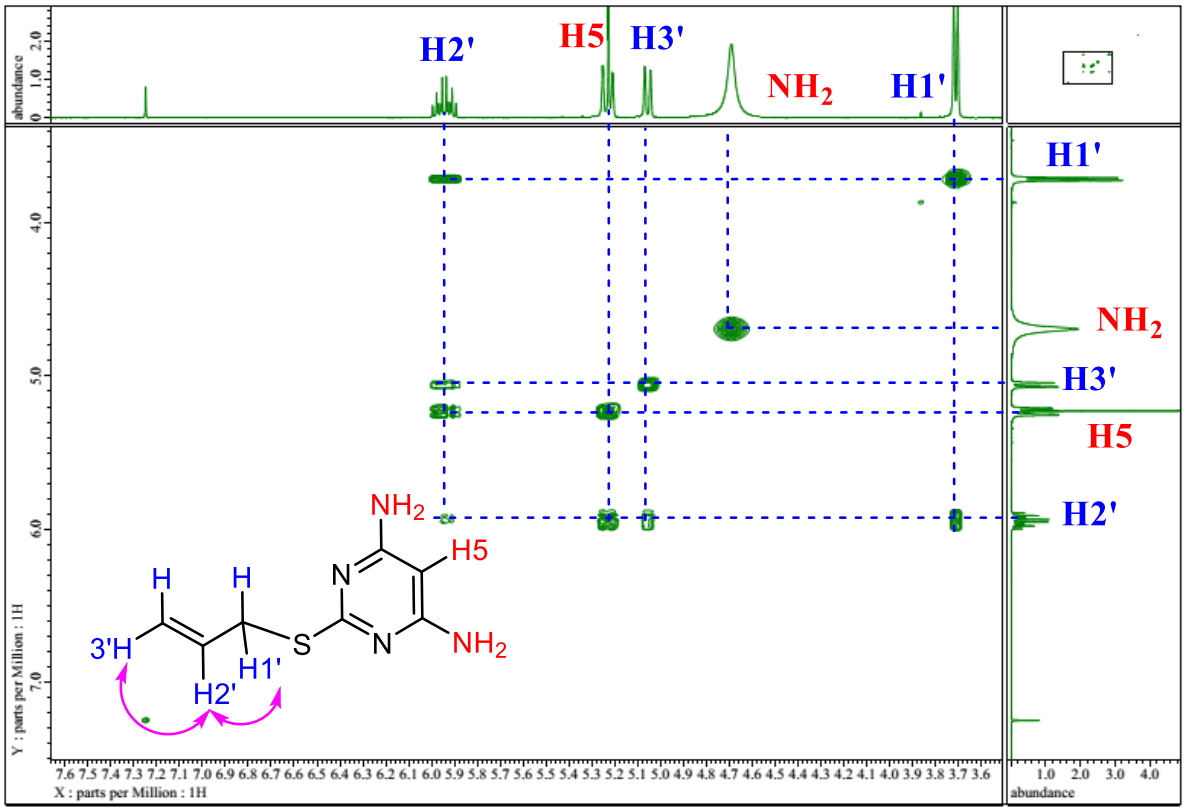
3-jadvalda DAMP ning Na li tuzi bilan to‘yinmagan alkil bromidlar o‘rtasidagi reaksiyalarga erituvchi, reaksiya davomiyligi va dastlabki reagentlarning nisbati reaksiya unumiga ta’sirini o‘rganish natijalari ko‘rsatilgan. Reaksiya DAMP ning Na li tuzi va to‘yinmagan alkil bromidlari o‘rtasida turli mol nisbatlarida 1:1, 1:1,2 va 1:2 hamda turli vaqt oralig‘ida 1 soat, 1,5 soat va 2 soat davomida olib borildi. Natijada, mol nisbati oshgan sari reaksiyaning unumdorligi ham oshadi. Reagentlar nisbati 1:2 bo‘lganda, kam vaqt sarflanib eng yuqori unumga erishildi.

4-jadval.

4,6-Diamino-2-merkaptopirimidin va allil va propargil bromidlar bilan reaksiyasidan olingan mahsulotlarning fizik-kimyoviy kattaliklari

(T.r.)	Mahsulot unumi %	T_S, °C	R_f, MeOH:$CHCl_3$ 1:5	Mahsulotning rangi
10	89	220,5-220,6	0,62	Jigar rangli kristal
11	90	119,9-120	0,61	Jigar rangli kristal

Reaksiya unumiga erituvchining ta’siri ham o‘rganildi, bunda metanol va DMFA ishlatildi: Metanol, qutubli proton erituvchi sifatida, o‘rtacha unum ko‘rsatdi. Ion oraliq mahsulotlar yoki o‘tish holatini barqarorlashtirish qobiliyati bu reaksiyaga yordam berdi, lekin unumni maksimal darajada oshirmadi. DMFA, qutbli aproton erituvchi sifatida, metanoldan ancha yuqori unum berdi. DMFAning qutbli tabiati dastlabki reagentlarni yaxshi eritdi va DAMPning nukleofilligini oshirib, reaksiyaning tez va yuqori unumda borishini ta’minladi.



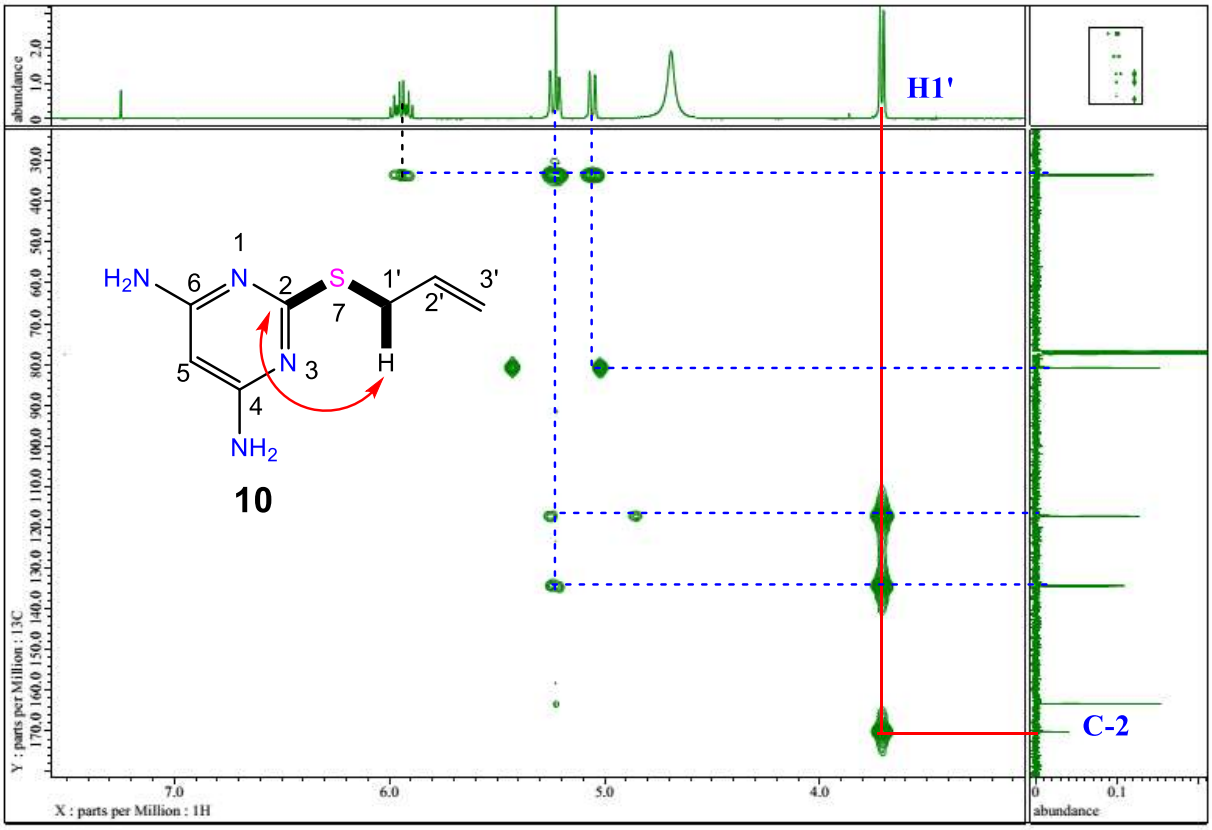
2-rasm. 10-Birikmaning COSY YaMR spektri tahlili.

10 birikmaning strukturasini aniqlashda COSY spektri asosiy ahamiyat kasb etadi. Ushbu spektr protonlarning o‘zaro bog‘lanishini aniqlashga va allil zanjiri tuzilishini tasdiqlashga imkon beradi.

COSY spektrida S-CH_2 guruhiga tegishli proton signali δ 3.71 m.u., allil guruhidagi CH proton signali esa δ 5.92 m.u.da joylashgan. Ushbu signallar o‘zaro

kross-cho‘qqi (cross-peak) hosil qilgani S-CH_2 guruhining allil zanjiriga bevosita bog‘langanligini tasdiqlaydi. Terminal vinil protonlar (CH_2) va markaziy allil proton (CH) o‘rtasida δ 5.93 m.u. hamda δ 5.21 m.u. da kuzatilgan kross-cho‘qqilar, allil zanjiridagi vinil va allil bog‘lanishlarning mavjudligini tasdiqladi. Kuzatilgan o‘zaro bog‘lanishlar (kross-cho‘qqilar) allil guruhining zanjirli strukturasini isbotladi va vinil bog‘lanishlarning o‘zaro ta’sir (splitting) xususiyatlarini ko‘rsatdi. Bu allil guruhining reaksiya natijasida oltingugurt atomi orqali pirimidin halqasiga bog‘langanligini tasdiqlaydi (2-rasm).

10 Birikmaning strukturasi HMBC usuli yordamida tasdiqlandi. Ushbu tahlil allil guruhi va pirimidin halqasi o‘rtasidagi asosiy uzoq masofadagi o‘zaro bog‘lanishlarni aniqlashga hamda molekula strukturasining bog‘lanishini isbotlashga yordam beradi. Proton YaMR spektrida 3,70 m.u. sohada kuzatilgan dublet signal, S-CH_2 metilen protonlariga tegishli bo‘lib, pirimidin halqasidagi C-2 atomi bilan kuchli uzoq masofadagi korrelatsiyani ko‘rsatdi. Bu kuzatuv allil guruhining oltingugurt (S) atomiga metilen orqali bog‘langanligini tasdiqlaydi.



3-rasm. 10-Birikmaning HMBC YaMR spektri tahlili.

Allil guruhidagi oxirgi vinil protonlari (CH=CH_2) metilen uglerod (S-CH_2) va markaziy allil uglerod bilan korrelyatsiya berdi. Allil guruhidagi terminal vinil protonlar o‘zining yaqin metilen uglerodi va oltingugurtga bog‘langan uglerod bilan kutilgan uzoq masofadagi korrelyatsiyalarni berdi. Bu allil guruhining oltingugurt atomiga bog‘lanishini tasdiqlaydi. NH_2 guruhiga tegishli protonlar (4- va 6-holatlarda) pirimidin halqasidagi tegishli uglerodlar bilan uzoq masofadagi

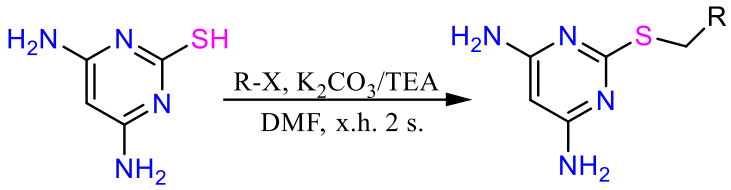
korrelatsiyalarni ko‘rsatdi. Bu pirimidin halqasining o‘rinbosar guruhlar joylashuvini tasdiqlaydi.

HMBC ma’lumotlari, ayniqsa, 3.70 m.u. sohadagi S-CH_2 dublet va C-2 o‘rtasidagi kuchli korrelyatsiya, DAMP allil bromid bilan reaksiyasi natijasida S-alkillanish muvaffaqiyatli amalga oshganligini isbotlaydi. Ushbu natijalar reaksiyaning azot (N) alkillanishi emas, balki oltingugurt (S) alkillanishi orqali amalga oshganligini ko‘rsatadi (3-rasm).

DAMPning to‘yinmagan alkil galogenidlar bilan olib borilgan reaksiya mahsulotlarini tuzilishi IQ, 1D, 2D YaMR, SXMS va YuSMS spektroskopik usulida tahlil qilindi.

4,6-Diamino-2-merkaptopirimidinning almashingan benzil galogenidlar bilan reaksiyalari

DAMPning almashingan benzil galogenidlar bilan reaksiyalari reagentlarning 1:1, 1:1,2, 1:1,5 nisbatlarida, xona haroratida, ishqor yordamida DMFA erituvchida ta’sirlanishidan quyidagi reaksiya tenglamasi bo‘yicha mahsulotlar hosil bo‘ldi.



1 **12-20**

Bu yerda, R-Benzil (**12**), 4-metilbenzil (**13**), 2,4-dimetilbenzil (**14**), 2,5-dimetilbenzil (**15**), 2,6-dimetilbenzil (**16**), 3-xlorobenzil (**17**), 4-xlorobenzil (**18**), 2,4-dixlorobenzil (**19**), 2,6-diftorobenzil (**20**).

DAMP tarkibida ikkita asosiy nukleofil markaz mavjud: Yuqoridagi tajribalar asosida DAMPning benzil galogenidlar bilan xona haroratida qutbli aproton erituvchi ishtirokida ta’sirlanishidan *S*-benzil hosilalar yuqori unumlar bilan olindi. Olingan natijalar 5-jadvalda keltirilgan.

DAMP ning benzil galogenidlar bilan 1:1,2, mol nisbatda xona haroratida erituvchi ishtirokida ta’sirlashuvi natijasida YuQX da DAMPning butunlay sarf bo‘lganligi kuzatildi, tiol guruhi hisobiga *S*-benzil mahsulotlar hosil bo‘ldi.

DAMPning almashingan benzil galogenidlar bilan 1:1,2 mol nisbatida xona haroratida qutibli aproton organik erituvchi ishtirokidagi reaksiyasidan **12** (85 %), **13** (85 %), **14** (90 %), **15** (87 %), **16** (82 %), **17** (66 %), **18** (51 %) hosilalar hosil bo‘ldi.

Ushbu tadqiqotda *S*-alkillangan 2-merkapto-4,6-diaminopirimidin hosilalarining hosil bo‘lish unumi tahlil qilindi. Unumning yuqori yoki past bo‘lishi benzil halqadagi o‘rinbosarlarning elektronodonor yoki elektronoakseptor xususiyatlariga bog‘liq ekanligi kuzatildi.

Jadval natijalaridan ko‘rinadiki, DAMP ning benzil galogenidlar bilan 1:1,2, mol nisbatda xona haroratida erituvchi ishtirokida ta’sirlashuvi natijasida YuQX da

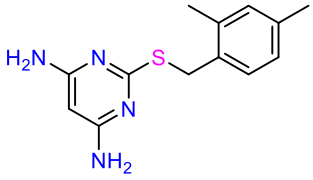
DAMPning butunlay sarf bo'lganligi kuzatildi. Tiol guruhi hisobiga *S*-benzil mahsulotlar hosil bo'ldi.

5-jadval.

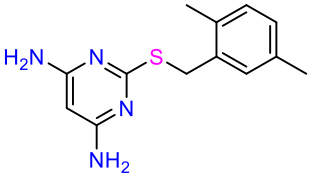
4,6-Diamino-2-merkaptopirimidinning benzil galogenidlar bilan reaksiyalariga dastlabki reagentlarning nisbati reaksiya unumiga ta'siri (DAMP:Benzil galogenid:K_2CO_3/TEA)

№	Benzilgalogenidlar K_2CO_3/TEA	1:1:2 Unum %	1:1,2:2 Unum %	1:1,5:2 Unum %	Reaksiya vaqti (s)
14	2,4-dimetilbenzil xlorid	81	**90**	**90**	2
15	2,5-dimetilbenzil xlorid	78	87	87	2
16	2,6-dimetilbenzil xlorid	70	78	82	2

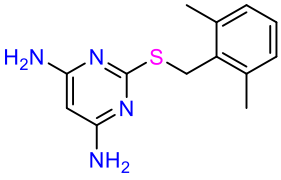
5-jadvalda keltirilgan kattaliklardan ma'lum bo'ladiki, DAMPning almashingan benzil galogenidlar bilan 1:1,2 mol nisbatida xona haroratida qutbli aproton organik erituvchi ishtirokidagi reaksiyasidan *S*-benzil hosilalar hosil bo'ladi.



14 (90%)



15 (87%)



16 (82%)

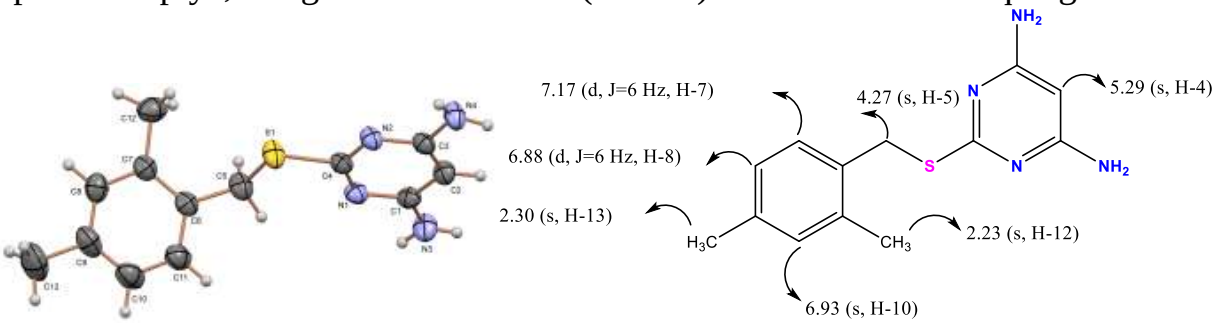
2,4-Dimetilbenzil molekulasida 2- va 4- holatlardagi metil guruhlari o'ziga nisbatan *orto*- hamda *para*-holatdagi C atomining elektron zichligini oshiradi. 2- va 4- holatdagi metil guruhining kelishilgan oriyentatsiyasi hisobiga benzil guruhidagi uglerod atomining elektron yetishmovchiligi keskin kamayadi hamda 2,4-dialmashingan benzil karbokationining barqarorligi eng yuqori bo'ladi. Shu sababli reaksiya S_N1 mexanizmi bo'yicha tez boradi, chunki reaksiya o'tish holati aynan barqaror karbokationning hosil bo'lishiga bog'liq. Barqaror karbokation qanchalik tez hosil bo'lsa va barqaror bo'lsa, reaksiya shunchalik tez boradi.

2,5-Dimetilbenzil molekulasida 2-holatdagi metil guruhi benzil guruhiga nisbatan kelishilgan holatda, ya'ni benzil kationining barqarorligi oshishiga xizmat qilsa, 5-holatdagi metil guruhi benzil guruhiga nisbatan *meta*- holatda joylashgan va uning elektronodonor sifatida ta'siri deyarli sezilmaydi. Shu sababli benzil guruhining barqarorligining oshishiga faqat bitta metil guruhi ta'sir ko'rsatadi xolos. Shu sababli, 2,4-dimetilbenzilgalogenidga nisbatan 2,5-dimetilbenzilgalogenid bilan boradigan reaksiya unumdorligi biroz pasaygan.

2,6-Dimetilbenzil galogenidda har ikkala metil guruhi ham elektronodonor sifatida kelishilgan holatda joylashgan bo'lsada, ularning har ikkalasining ham *orto*- holatda joylashuvi katta hajmli nukleofil reagent DAMPning oltingugurt nukleofilining hujumini qiyinlashtiradi. Natijada molekulaning koplanarligi (bir tekislikda yotishi) buziladi va har ikkala alkil guruhining benzil guruhiga ko'rsatadigan musbat induksion ta'siri deyarli yo'qoladi. Shu sababli reaksiya S_N2 mexanizmi bo'yicha boradi hamda reaksiya unumi 2,4- va 2,5-dialmashingan

benzilgalogenidlar bilan boradigan reaksiyalarga nisbatan past bo‘lishiga olib keldi.

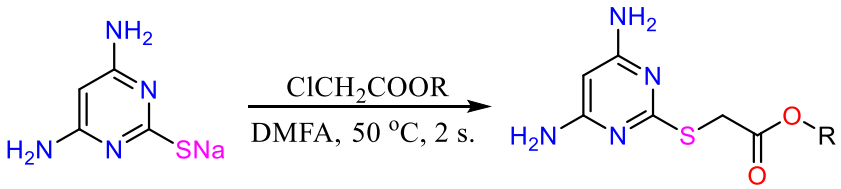
Sintez qilingan birikmalarning individualligi YuQX usuli yordamida aniqlangan. Buning uchun metanol:xloroform (1:5) sistemasi tanlandi va sintez qilingan birikmalarning R_f qiymatlari aniqlangan. Sintez qilingan *S*-benzil hosilalarning tuzilishi IQ, YuSMS, YuSSX, ^{1}H, ^{13}C, HMBC YaMR spektroskopiya, rentgen tuzilish tahlili (4-rasm) usullari bilan tasdiqlangan.



4-rasm. 14-Birikmaning kristal tuzilishi va ^{1}H YaMR spektr tahlili.

4,6-Diamino-2-merkaptopirimidinning *S*-alkil atsetoefir hosilalarini o‘rganish

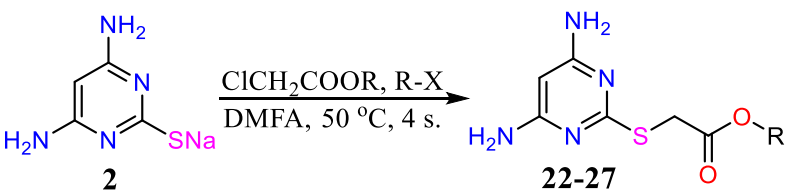
S-Alkillangan atsetoefir hosilalarini sintez qilishda DAMPning yuqori nukleofil xususiyatlari hisobga olindi. Reaksiya monoxlorsirka kislotasining metil va etil efirlari bilan DMFA erituvchisida 50 °C haroratda ikki soat davomida olib borildi. Metil hosila 75 % unum bilan olindi, etil hosila esa 67 % unum bilan sintez qilindi. Ushbu farq fazoviy to‘siq va elektron ta’sirlar bilan izohlanadi. Metil guruhi kichikroq bo‘lgani uchun elektrofil markaz (xlormonosirka kislota efiri) bilan reaksiyaga kirishishi osonlashadi. Etil guruhi esa biroz kattaroq fazoviy ta’sirga ega bo‘lib, tioanionning elektrofilga hujum qilish qobiliyatini pasaytiradi, natijada unum nisbatan kamayadi. Bundan tashqari, DMFA erituvchisi qutbli aproton erituvchi, nukleofil S^- ionining reaktivligini oshirdi va *S*-alkillanishni tezlashtirdi.



2 **21-22**

R = Me, Et

Shuningdek, 4,6-diamino-2-merkapto-pirimidin, monoxlorsirka kislotaning natriyli tuzi va alkil galogenidlar bilan bir bosqichli (*one-pot*) reaksiyasi amalga oshirildi. Natijada, *S*-alkillangan atsetoefir hosilalari sintez qilindi.



2 **22-27**

R = allil (**23**), propargil (**24**), benzil (**25**) 2,4-dimetilbenzil (**26**), 2,5-dimetilbenzil (**27**); X = Br, Cl.

Dissertatsiyaning **“Sintez qilingan moddalarning biologik xossalari”** deb nomlangan **uchinchi bobida** tadqiqot natijasida olingan moddalarning antibakterial faolligi, saratonga qarshi faolligi va insektidsitlik faolligi keltirilgan.

6-jadval

Sintez qilinga *S*-alkilatsetoefir hosilalarining reaksiya natijasida olingan unumlari (DAMP Na:$ClCH_2COONa$:alkil:galogenid)

№	Mahsulot unumi %	R_f metanol:xloroform 1:5	Reagentlar nisbari	Reaksiya vaqti	Birikmaning rangi
21	75	0,62	1:1	2	jigar rangli
22	67	0,62	1:1	2	jigar rangli
23	66	0,62	1:1:1,2	4	jigar rangli
24	61	0,62	1:1:1,2	4	jigar rangli
25	85	0,62	1:1:1,2	4	jigar rangli
26	82	0,62	1:1:1,2	4	Och sariq
27	80	0,62	1:1:1,2	4	Och sariq

Antibakterial faolligi.

15 Birikma turli grammusbat va grammanfiy bakteriyalarga nisbatan antibakterial faollikka ega. Ushbu birikmaning biologik faolligi bakteriya hujayra devorining tuzilishi va membrana o‘tkazuvchanligiga bog‘liq.

Grammusbat bakteriyalar kuchli murein qatlamiga ega bo‘lib, ular **15** birikmaning ta’siriga nisbatan sezgirlik darajasini ko‘rsatdi. *S. aureus* 15 ga nisbatan *B. subtilis* ga qaraganda yuqori sezgirlik namoyon etdi (18 mm va 16 mm), bu esa **15** birikmaning *S. aureus* membrana tuzilishiga ko‘proq ta’siri aniqlandi.

7-jadval

2-{(2,5-Dimetilbenzil)tio}pirimidin-4,6-diaminning antibakterial faolligi

№	Grammusbat bakteriyalar		Grammanfiy bakteriyalar		*Candida albicans*
	Bacillus subtilis	***Staphylococcus aureus***	***Escherichia coli***	***Pseudomonas aeruginosa***	
15	16 mm	18 mm	20 mm	17 mm	15 mm

Grammanfiy bakteriyalar tashqi membrana bilan himoyalangan bo‘lib, bu ularni antibiotik va boshqa kimyoviy moddalar ta’siriga nisbatan chidamliroq qiladi. Biroq **15** birikma ***E. coli*** ga nisbatan 20 mm li ingibisyon zonasi bilan eng yuqori antibakterial ta’sir ko‘rsatdi, *P. aeruginosa* esa nisbatan biroz kamroq sezgir bo‘lib, 17 mm inhibisyon zona qayd etdi.

Candida albicans (15 mm) ham **15** moddaga nisbatan sezgirlik namoyon etdi. Bu natija **15** birikmaning fungisitlik faollikka ham ega ekanligini ko‘rsatadi, ammo bakteriyalarga nisbatan ta’siri biroz past.

Shunday qilib, **15** birikmaning Escherichia coli ga nisbatan eng yuqori antibakterial faollikni namoyon etdi (20 mm), undan keyin S. aureus (18 mm), P. aeruginosa (17 mm), B. subtilis (16 mm) va C. albicans (15 mm) bakteriyalariga nisbatan ta’sir ko‘rsatdi.

Rakka qarshi faolligi

Dunyo bo‘ylab insonlar o‘limining asosiy sabablaridan biri saraton kasalligidir. Saraton tufayli eng yuqori o‘lim holatlari oshqozon, jigar, bachadon bo‘yni, ko‘krak, prostata, o‘pka va yo‘g‘on ichak saratoni bilan bog‘liq. 2-Tiopirimidin birikmalarning saratonga qarshi biologik faolliklarni namoyon qilishi ma’lum.

Analiz qilingan moddalarning barchasi (**10**, **11**, **14**, **15**, **24**, **25**,) HeLa hujayra liniyasiga turli darajada sitotoksik faollik namoyon qilgan. Moddalarning hujayralarni o‘ldirish darajasi ularning konsentratsiyasiga bog‘liq bo‘lib, yuqori konsentratsiyada (100 mkg/ml) sitotoksik ta’sir maksimal darajada kuzatilgan (8-jadval).

8-jadval.

4,6-Diamino-*S*-alkiltiopirimidin hosilalarining HeLa hujayrasini ingibirlash darajasi ularning konsentratsiyasiga bog‘liqligi

№	Mkg/ml / Namunalar	Tirik hujayralar			Ingibirlash		
		100	**10**	**1**	**100**	**10**	**1**
1.	**10**	86,96	98,15	97,91	13,04	1,85	2,09
2.	**11**	94,96	97,05	98,28	5,04	2,95	1,72
3	**14**	55,23	71,09	74,78	44,77	28,91	25,22
4	**15**	**4,42**	**79,95**	**84,99**	**95,76**	**20,05**	**15,01**
5.	**26**	67,90	80,57	83,52	32,10	19,43	16,48
6	**27**	80,44	84,50	87,21	19,56	15,50	12,79
7.	**Sisplatin**	**11,07**	**85,49**	**104,43**	**88,93**	**14,51**	**4,18**
8.	**Doksorubitsin**	**29,64**	**79,09**	**90,28**	**70,36**	**20,91**	**9,72**

Eng yuqori antiproliferativ faollikni **15** modda namoyon qilgan bo‘lib, 100 mkg/ml konsentratsiyada sitotoksik ta’siri 95,76 %ni tashkil qilgan. Ushbu moddaning 10 va 1 mkg/ml konsentratsiyalarida hujayra o‘sishini ingibirlash darajasi mos ravishda 20,05 % hamda 15,01 %ga kamaygan. Bu esa uning konsentratsiyasi bilan bog‘liq sitotoksik ta’sirga ega ekanligini ko‘rsatdi.

Bundan tashqari, **14** birikma ham yuqori sitotoksiklik namoyon qilgan bo‘lib, 100 mkg/ml kontsentratsiyada hujayralarni 44,77 %ga ingibirlagan. **25** modda esa 100 mkg/ml konsentratsiyada 32,10 % sitotoksik ta’sir ko‘rsatgan. Bu esa **24** ga qaraganda biroz past, ammo sezilarli darajada antiproliferativ ta’sirga egaligini anglatadi.

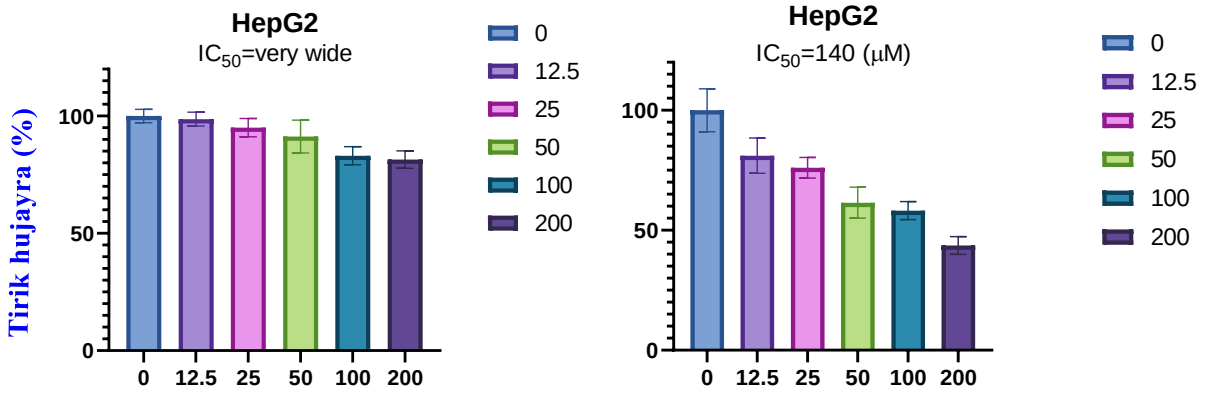
Tadqiqotda ishlatilgan ijobiy nazorat vositalari – sisplatin va doksorubitsin ham sitotoksiklik darajasini ko‘rsatib berdi. Sisplatin 100 mkg/ml konsentratsiyada 88,93 % hujayralarni ingibirlagan, bu uning samarali sitotoksik vosita ekanligini

tasdiqlaydi. Doksorubitsin esa 70,36 % sitotoksik ta’sir ko‘rsatdi, bu esa olingan moddalarning ayrimlari bilan solishtirilganda biroz pastroq natijani ifodalaydi.

Natijada, ba’zi *S*-alkillangan 4,6-diamino-2-merkaptopirimidin hosilalari HeLa hujayralariga qarshi sezilarli sitotoksiklik namoyon qilgan. Ayniqsa, **15** va **14** moddalari istiqbolli sitotoksik vositalar sifatida ko‘rish mumkin.

4,6-Diaminomerkaptopirimidin-*S*-benzil birikmalarning jigar saratoni (HepG2) hujayra liniyasiga nisbatan antiproliferativ faolligi

HepG2 hujayralari uchun **14** modda ta’sirida IC_{50} qiymati tanlangan konsentratsiya diapazonida aniqlanmadi va kutilgan qiymat juda keng bo‘lgani sababli qayd etilmadi. Biroq hujayra hayotiyligining kamayish tendensiyasi kuzatildi: **14** birikma konsentratsiyasi oshgan sari hujayra hayotiyligi proporsional ravishda pasaydi. Masalan, **14** ning 50 µM konsentratsiyasida hujayra hayotiyligi 10 %ga kamaydi, 200 µM da esa 20 %ga pasayishi kuzatildi.



14 Birikmaning 24 s. ta'sirlashuvi

15 Birikmaning 24 s. ta'sirlashuvi

4-rasm. 14 va **15** birikmalarning inson jigar saratoni hujayra liniyasiga sitotoksik ta’siri natijalari.

Boshqa tomondan, **15** birikmasi esa sitotoksiklik faollik namoyon etgan. Hayotiylik 12.5 µM kontsentratsiyada 80 % atrofida saqlangan bo‘lsa, konsentratsiya oshishi bilan hayotiylik pasayib borgan. 200 µM da tirik hujayra 40 % atrofida bo‘lib, IC_{50} 140 µM ga teng ekani aniqlangan. Bu shuni anglatadiki, **15** HepG2 hujayralarida **14** birikmaga qaraganda yuqori sitotoksik faollikka ega. **14** Nisbatan kamroq toksik bo‘lib, **15** esa o‘rtacha darajada sitotoksiklik namoyon qildi. Shu sababli, **15** moddaning o‘simtaga qarshi potensialini chuqurroq o‘rganish lozim, jumladan, uning apoptoz yoki nekroz chaqirish qobiliyati ham baholanishi kerak.

Insektidsitlik faolligi

DAMPning *S*-alkil hosilalarining insektitsid faolligini baholash maqsadida *Helicoverpa zea* va *Spodoptera frugiperda* hujayra liniyalaridan foydalanildi. Moddalar hujayralarga 10 va 100 µM/ml konsentratsiyalarda ta’sir ettirilib, ularning insektitsid faolligi MTT-test yordamida baholandi. Olingan natijalar tahlil qilinganda, turli birikmalar har xil darajada insektitsid faollik ko‘rsatgani aniqlandi. Eng samarali moddalardan biri – **24** birikma bo‘lib, u *Spodoptera*

frugiperda hujayralarida yuqori faollik ko‘rsatdi. **4** birikma ham *Spodoptera frugiperda* hujayralarida faol bo‘ldi, shuningdek, *Helicoverpa zea* hujayralarida 10 μM/ml konsentratsiyada 65 %, 100 μM/ml da esa 70,1 % faollik ko‘rsatdi. **5** modda esa *Spodoptera frugiperda* hujayralarida insektitsid faollik ko‘rsatmadi (0 %).

Nazorat sifatida ishlatilgan “*Bagira*” 20 % insektitsidi har ikkala hujayra liniyasida yuqori samaradorlikni ko‘rsatdi va sinov moddalari uchun taqqoslash mezoni sifatida foydalanildi (9-jadval).

Ushbu tadqiqot natijalari hasharotlarga qarshi samarali birikmalarni aniqlash va kelajakda insektitsid sifatida foydalanish mumkin bo‘lgan istiqbolli moddalarning tanlab olinishi uchun ilmiy asos yaratadi.

9-jadval

4,6-Diamino-*S*-alkiltiopirimidin hosilalarining insektitsidlik faolligi

№	***Helicopvera zea***		***Spodotera frugiperda***	
	10 mkM/ml	100 mkM/ml	10 mkM/ml	100 mkM/ml
6	65 %	70,1 %	72.7 %	88,2 %
7	29,65 %	38.1 %	0 %	0 %
12	42,9 %	43,8 %	82 %	85 %
14	51,7 %	61,03 %	85 %	61 %
15	9,5 %	19 %	14 %	24 %
26	26,9 %	72,9 %	83 %	67 %
27	0 %	54,7 %	25 %	36.7 %
“*Bagira*” 20%	**79,3 %**	**89,6 %**	**81.5 %**	**91.3 %**

Dissertatsiyaning **to‘rtinchi bobida** tajribaviy qism, birikmalarning kimyoviy modifikatsiyasi va sintez qilish usullari keltirilgan. Birikmalarni indentifikatsiya qilish va tuzilishini aniqlash usullari: xromatografiya (SXMS, YuSM, YuQX), spektroskopiya (IQ-, ^{1}H- va ^{13}C YaMR) natijalari keltirilgan.

Xulosalar

1. Ilk bor DAMPning -propargil, -geptil, -nonil, -4-metilbenzil -2,4-dimetilbenzil, -2,5-dimetilbenzil, -2,6-dimetilbenzil, -2,6-diftorobenzil, -2,4-dixlorobenzil, -3-xlorobenzil, -4-xlorobenzil o‘rinbosar tutgan yangi hosilalari sintez qilindi, mahsulot unumiga turli omillar ta’siri aniqlandi, jarayonlar borishi optimallashtirildi.

2. DAMPning –metil, -etil, (*one pot* usulida) -allil, -propargil, -benzil, -2,4-dimetilbenzil, -2,5-dimetilbenzil radikal tutgan tioalkilatsetoefirlarning yangi hosilalari sintezi amalga oshirildi, maqbul sharoitlar topilgan va zamonaviy fizik kimyoviy usullarda struktura formulasi tasdiqlandi.

3. *S*-Alkil hosilalarida zanjir uzunligi ortishi bilan reaksiya unumi kamaydi, harorat 20-70 ^{0}C gacha ortganda reaksiya unumi ortib bordi. Butil, pentil, geksil hosilalar uchun harorat 50 ^{0}C da, geptil, nonil hosilalar uchun 70 ^{0}C da monomahsulot hosil bo‘lishi aniqlandi.

4. DAMPning allil, propargil hosilalari sintezi proton va aproton erituvchilarda olib borilganda reaksiya unumi aproton erituvchilarda yuqori ekanligi aniqlandi. DAMPning Na tuzi bilan allil, propargil bromidlar nisbati 1:2 bo‘lganda reaksiya tezligi va reaksiya unumi yuqoriligi (90 %) isbotlandi.

5. DAMP bilan olib borilgan reaksiyalar asosida, elektronodonor o‘rinbosarlar tutgan dimetilbenzil xloridlarning nukleofil almashinish reaksiyalariga kirishish qobiliyati o‘rganildi. Natijalarga ko‘ra, bu faollik 2,4-dimetilbenzil xlorid > 2,5-dimetilbenzil xlorid > 2,6-dimetilbenzil xlorid tartibida kamayishi aniqlandi. Bu esa, o‘rinbosarlarning sterik va elektron ta’siri reaksiyaning borishiga sezilarli darajada ta’sir ko‘rsatdi.

6. DAMPning 2,5-dimetilbenzil almashingan hosilasi grammanfiy bakteriyalar *(Escherichia coli 20 mm)* grammusbat bakteriyaga nisbatan foalligi yuqori ekanligi aniqlandi. *S*-Benzil hosilalarining HepG2 (IC_{50} 140 μM) saraton hujayralariga kam faollik va Hela (4,42 μM) inson saraton hujayralariga nisbatan yuqori sitotoksik konsentratsiyalari aniqlanib, kimyoterapiyada qo‘llaniladigan sisplatin dori vostasidan ham yuqori faollik namoyon qilgan, shuningdek, *S*-alkil hosilalarining insektitsidlik xususiyatlari ko‘ra, geptil hosila (70 %) *makkajo‘xori sofikasiga* eng yuqori insektitsid faollikka ega ekanligi tasdiqlandi.

SCIENTIFIC COUNCIL No. DSc. 03/30.12.2019.K.01.03 FOR THE AWARD OF ACADEMIC DEGREES AT NATIONAL UNIVERSITY OF UZBEKISTAN

NATIONAL UNIVERSITY OF UZBEKISTAN

SALIEVA GULRUKH BAKHODIROVNA

SYNTHESIS OF *S*-ALKYL PRODUCTS BASED ON 4,6-DIAMINO-2-MERCAPTOPYRIMIDINE AND THEIR BIOLOGICAL ACTIVITY

02.00.03-Organic chemistry (chemical sciences)

DOCTOR OF PHILOSOPHY IN CHEMISTRY (PhD)
ABSTRACT OF THE DISSERTATION

Tashkent-2025

The theme of the Doctor of Philosophy (issertation in chemical sciences is registered in the Higher Attestation Commission under linistry of Higher Education, Science and Innovation of the Republic of Uzbekistan under the number B2024.4PhD/K622.

The dissertation was carried out at National University of Uzbekistan.

The abstract of the dissertation was posted in three (Uzbek, English, Russian (resume)) languages on the website of the Scientific Council at www.ispm.uz and on the website of "ZiyoNet" Information and Educational Portal at www.ziyonet.uz.

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Leading organization:	**Tashkent pharmaceutical institute**

The dissertation will be defended on 05.06. 2025 at 9[00] hours at the meeting of the Scientific Council No. DSc. 03/30.12.2019.K.01.03 at the at the National University of Uzbekistan (Address: 100174, Tashkent, University street, 4th house). Tel.: (99871) 227-12-24, fax: (99824) 246-02-24, e-mail: ilmiy_kengash@nuu.uz).

The dissertation can be viewed at the Information Resource Center of the National University of Uzbekistan (registered with the number 98). Address: (100174, Tashkent, University street, 4th building, phone: (+99871) 246-67-71.

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INTRODUCTION

(Abstract of Doctor of Philosophy (PhD) thesis)

Relevance and importance of the dissertation topic. Nowadays, pyrimidine derivatives are widely used in medicine and pharmaceuticals as drugs against various diseases, and in the agro-industrial sector as herbicides and fungicides. In particular, amino derivatives of pyrimidine are used in anticancer drugs such as *gemcitabine, crizotinib, acalabrutinib, and imatinib*. Developing analogs of these drugs, improving their synthesis methods, and applying them in practice have significant practical importance.

Worldwide, extensive research has been conducted on developing efficient methods for synthesizing *S*-alkyl and *S*-acetamide compounds based on DAMP, as well as proposing new catalysts for these reactions. In particular, alkylation reactions of DAMP with aliphatic, aromatic, and heterocyclic halogenated derivatives, as well as reactions involving monochloroacetic acid amides, metal complex compounds, and nanocatalysts, hold significant scientific importance.

In recent years, important achievements have been made in our country in obtaining natural and synthetic organic compounds aimed at ensuring the interconnection between education and industry and producing import-substituting products based on local raw materials. In the development strategy of new Uzbekistan for 2022–2026, tasks are outlined to "ensure the sustainability of the national economy and continue industrial policy aimed at increasing the share of industry in the gross domestic product by 1.4 times through increased industrial production."[1]In this regard, finding convenient methods for synthesizing *S*-alkyl derivatives of aminomercaptopyrimidine, analyzing their structures using modern physicochemical methods, identifying the main factors affecting the processes and the reaction patterns, studying the physicochemical and biological properties of the obtained compounds, and creating biologically active substances containing new pharmacophore groups are of significant scientific and practical value.

This dissertation contributes, to a certain extent, to the implementation of the tasks defined in the Resolution No. PQ-4992 of the President of the Republic of Uzbekistan dated February 13, 2021, "On further reforming and financially improving chemical industry enterprises and developing the production of high value-added chemical products," 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," and Presidential decree No. PF-60 dated January 28, 2022, "On the development strategy of new Uzbekistan for 2022–2026," as well as other relevant regulatory documents.

[1] Decree of the President of the Republic of Uzbekistan No. PF-60 dated July 6, 2022, “On the Development Strategy of New Uzbekistan for 2022–2026.”

Compliance of the research with the priority areas of science and technology development in the Republic. This research has been conducted in accordance with the VII priority areas of the development of science and technology in the republic: chemical technologies and nanotechnologies.

Degree of study of the problem. In many developed countries around the world, research on the synthesis of *S*-alkyl products based on 2-mercaptopyrimidine and their biological activity is being actively conducted. In particular, foreign scientists, such as M. A. Yusuf and his group have studied the antibacterial and fungicidal properties of *S*-alkyl derivatives based on amino-2-mercaptopyrimidine. They analyzed the synthesis of new biologically active compounds and their effectiveness against microorganisms and fungi. R.K.M. Mahmoud researched the synthesis of *S*-alkyl 6-amino-2-mercaptopyrimidine and its antibacterial properties, analyzing its antifungal effects against microorganisms (bacteria, viruses). Researchers like Xiu Zhang, A. Tariq, M. George, N. Mikhail, M. Abdullahi, M. Hassan, and B. Luis have worked on optimizing synthesis processes for new drugs, studying the anticancer and antiviral effects of *S*-alkyl compounds, as well as their toxicological analyses.

In our country, significant research has been conducted by Uzbek scientists on natural and synthetic pyrimidines, contributing to the development of this field. For example, academician S.Yu. Yunusov and his colleagues, professors Kh.M. Shakhidoyatov, N.D. Abdullaev, B.Dj. Elmurodov, V.I. Vinogradova, Kh.U. Khodaniyozov, Kh.A. Bozorov, and others have carried out scientific studies on the extraction of pyrimidine derivatives from plants, as well as the general synthesis and chemical properties of these compounds.

Analysis of the literature shows that despite the existence of extensive experimental data on the synthesis of *S*-alkyl products of aminomercaptopyrimidines, the synthesis of their *S*-allyl (propargyl) and *S*-alkyl acetoester derivatives has not been studied. Therefore, investigating the reactions of mercaptopyrimidine with alkyl halides and determining the biological activity of the synthesized compounds is of particular scientific interest.

Relevance of the dissertation topic to the research plans of the higher education institution. The dissertation research was conducted within the framework of the scientific research projects of the National University of Uzbekistan, specifically the OT-F-7-52 (OT-F-7-50, OT-F-7-56, OT-F-7-58) project "Laws of interaction and reactivity of organic and inorganic substances of different natures, and the synthesis of new compounds with specific complex properties" (2017-2020) and AM-FZ-2019081452 “Development of a technology for the synthesis of cyclohexane based on ethylene” (2020–2022), which falls under its fundamental research projects.

The aim of research work. It consists in the synthesis of *S*-alkyl derivatives based on 4,6-diamino-2-mercaptopyrimidine and the investigation of their biological activity.

Research Tasks.

synthesize new *S*-alkyl derivatives of 4,6-diamino-2-mercaptopyrimidine (DAMP) under various conditions;

conduct *S*-allylation (propargylation) reactions of DAMP with unsaturated allyl (propargyl) bromides in the presence of proton and aproton solvents;

investigate the reactivity of DAMP in *S*-benzylation (nucleophilic substitution) reactions with substituted benzyl halides;

determine the relative reactivity of alkyl halides in *S*-alkylation reactions with DAMP, and study the effects of temperature, reaction duration, solvent type, and the ratio of reactants on the reaction course;

synthesize new thioalkyl acetoester derivatives of DAMP using alternative methods;

confirm the structure of the synthesized compounds using modern physicochemical research techniques;

determine the biological activity of the synthesized compounds.

Object of the research. The object of the research includes the *S*-alkyl derivatives of 4,6-diamino-2-thiopyrimidine (DAMP), namely: sodium salt, *n*-butyl, *n*-pentyl-, *n*-hexyl-, *n*-heptyl-, *n*-nonyl-, allyl-, propargyl-, benzyl-, 4-methylbenzyl-, 2,4-dimethylbenzyl-, 2,5-dimethylbenzyl-, 2,6-dimethylbenzyl-, 3-chlorobenzyl-, 4-chlorobenzyl-, 2,4-dichlorobenzyl-, and 2,6-difluorobenzyl-alkylthio derivatives. Additionally, the methyl-, ethyl-, allyl-, propargyl-, benzyl-, 2,4-dimethylbenzyl-, and 2,5-dimethylbenzyl- thioalkyl acetoester derivatives of DAMP are also considered as objects of the study.

Subject of the research. The subject of the research includes nucleophilic substitution reactions at the sulfur atom of DAMP, and the determination of the physicochemical and biological properties of the *S*-alkyl, *S*-unsaturated alkyl, *S*-benzyl, and *S*-alkyl acetoester reaction products.

Research methods. Modern organic chemistry methods, including spectrometric (high-resolution mass spectrometry (HRMS), high-performance liquid chromatography (HPLC) liquid chromatography-mass spectrometry (LCMS)), spectroscopic (NMR, IR, X-ray structural analysis (XRD), thin layer chromatography (TLC)), and biological research methods, have been applied.

Scientific novelty of the research includes the following:

for the first time, the synthesis of DAMP derivatives with *n*-heptyl-, *n*-nonyl, allyl-, propargyl-, 4-methylbenzyl-, 2,4-dimethylbenzyl-, -2,5-dimethylbenzyl-, 2,6-dimethylbenzyl-, 3-chlorobenzyl-, 4-chlorobenzyl-, 2,4-dichlorobenzyl-, and 2,6-difluorobenzyl- has been carried out;

for the first time, DAMP derivatives with allyl-, propargyl-, -benzyl-, 2,4-dimethylbenzyl-, and 2,5-dimethylbenzyl- radicals were obtained using a "*one-pot*" synthesis method, resulting in thioalkyl acetoester compounds;

It was observed that with an increase in the chain length of *S*-alkyl derivatives, the reaction yield decreased. However, as the temperature increased from 20 to 70°C, the reaction yield improved, for butyl, pentyl, and hexyl derivatives, the

reaction produced a mono substituted product at 50°C, whereas for heptyl and nonyl derivatives, it occurred at 70°C;

when synthesizing the allyl and propargyl derivatives of DAMP in proton and aproton solvent, it was found that the reaction yield was higher in aproton solvent. The reaction speed and yield were also higher (90%) when the ratio of DAMP sodium salt to allyl and propargyl bromides was 1:2;

It was found that the ability of dimethyl-substituted benzyl derivatives containing electron-donating substituents to undergo nucleophilic substitution reactions with DAMP decreases in the following order: 2,4-dimethylbenzyl chloride < 2,5-dimethylbenzyl chloride < 2,6-dimethylbenzyl chloride;

The structures of the S-alkyl derivatives obtained based on DAMP were confirmed using mass spectrometry, NMR, IR spectroscopy, and X-ray diffraction methods.

15 compound (4.42 μM) exhibited 2.5 times more activity than the standard "cisplatin" (11.07 μM) the against cervical cancer cells (HeLa), leading to 95.8% cell death;

The practical results of the research are as follows:

optimum synthesis methods for S-alkylation reactions based on DAMP have been identified;

for the first time, methods for obtaining mono products in the allyl and propargyl bromide alkylation reactions of DAMP have been proposed;

the first-time synthesis methods for *S*-alkyl acetoester derivatives of DAMP have been developed.

for the first time, the crystal structure and all crystallographic parameters of 2-{(2,4-dimethylbenzyl)thio}pyrimidine-4,6-diamine have been determined and included in the International Cambridge crystallographic data centre (CCDC) database.

The reliability of the research results is confirmed by the data obtained from chromatographic and physicochemical methods, including IR, HRMS, HPLC, LCMS, ^{1}H, ^{13}C, HMBC, HSQC, COSY, and NMR spectroscopy, XRD analysis, and biological methods. Additionally, the reliability is supported by the publication of the research findings in several international scientific journals.

The scientific significance of the research results lies in the fact that selective *S*-alkylation of DAMP with alkyl halides, unsaturated alkyl halides, substituted benzyl halides, and monochloroacetic acid has been successfully achieved. Systematic studies on nucleophilic substitution reactions under various conditions have been conducted, and key factors affecting the direction of the reactions have been identified.

The practical significance of the research results is evident in the identification of *S*-alkyl compounds exhibiting high cytotoxic activity among the synthesized compounds, for which optimal synthesis methods have been developed. A total of 23 substances were synthesized, of 17 of them are new compounds, and biological activity was demonstrated for several synthesized substances. The novelty and

crystal structure of 2-{(2,4-dimethylbenzyl)thio}pyrimidine-4,6-diamine were confirmed through X-ray diffraction analysis, and it was included in the International Cambridge crystallographic data centre (CCDC) database.

Implementation of the research results. Based on the scientific results obtained from the reactions of DAMP with alkyl halides:

XRD results of 2-{(2,4-dimethylbenzyl)thio}pyrimidine-4,6-diamine have been included in the Cambridge Crystallographic data centre (CCDC) database, with the entry number 2431935 (dated March 17, 2025). As a result, this has enabled the identification of the structures of new compounds that are part of the substituted thiopyrimidine derivatives.

In the fundamental project titled "Blocking of aquaporin channels using biologically active compounds to limit cancer cell proliferation: experimental studies at the molecular level", carried out by the "Innovative pharmaceutical compounds" research laboratory at Tashkent Pharmaceutical institute (2022-2024). This project was supported by the Ministry of higher education, science, and innovation of Uzbekistan (reference number: 03/17-668, dated March 14, 2025).

As a result, *S*-alkyl compounds synthesized from DAMP have demonstrated inhibition activity against liver cancer (HepG2) cells.

Approval of the research results. The results of this research have been presented and discussed at 4 scientific and practical conferences, including 2 international and 2 national events.

Publication of research results. A total of 9 scientific works has been published based on the dissertation, of which 5 articles have been recommended for publication in scientific journals that feature key research findings for doctoral dissertations, as recommended by the Higher Attestation Commission of the Republic of Uzbekistan. Among these, 2 articles have been published in national journals and 3 in international journals.

Structure and volume of the dissertation. The dissertation consists of an introduction, 4 chapters, conclusion, a list of references, and appendices. The total length of the dissertation is 120 pages[1].

MAIN CONTENT OF THE DISSERTATION

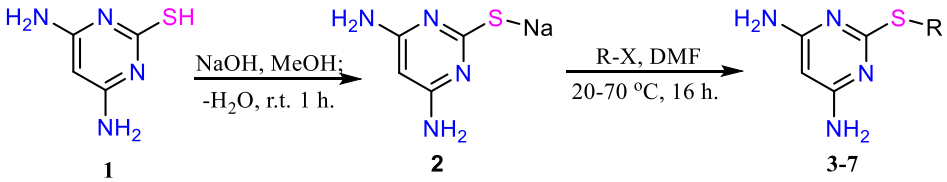
In the introduction, the relevance and importance of the research are discussed, including the goals and objectives of the study. The object and subject of the research are described, and the alignment of the research with the priority directions of national science and technology development is indicated. The scientific novelty and practical significance of the research results are presented, and the application of these results in practice is highlighted. Information about the published works and the structure of the dissertation is also provided.

[1] *The author expresses sincere gratitude to Professor A.D. Matchanov of the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan for his support in the completion of this dissertation.*

The first chapter of the dissertation, titled **"Synthesis of substituted pyrimidines, their properties, and areas of application"**, includes a literature review. This section analyzes various pyrimidine derivatives, focusing on their synthesis, modification, and biological activity. The current state of the literature regarding these topics is reviewed and evaluated.

In the second chapter of the dissertation, titled **"Synthesis of *S*-alkyl derivatives based on 4,6-diamino-2-mercaptopyrimidine (discussion of the obtained results)"**, various reactions involving DAMP are discussed. These reactions include *S*-alkylation, *S*-allylation (propargylation), *S*-benzylation, and *S*-acetylation with ethyl ester. The reactions were carried out under different conditions, and the chemical structure of the resulting compounds was analyzed. The results of chromatography, spectroscopy (IR, ^{1}H, ^{13}C, HSQC, and HMBC NMR), HRMS, LCMS and XRD are presented in the dissertation.

S-Alkylation products were synthesized from DAMP and alkyl halides, following the general reaction scheme:



1 **2** **3-7**

Here: R=C_4H_9 (**3**); C_5H_{11} (**4**); C_6H_{13} (**5**); C_7H_{15} (**6**); C_9H_{19} (**7**).

This chapter provides a detailed discussion on the synthesis conditions, the factors influencing the reaction efficiency, and the structural analysis of the products using advanced techniques.

During the experiments, the effect of temperature on the reaction yield was studied. The initial reagent molar ratio was 1:1.2, with methanol (MeOH) used as the solvent in the first stage and dimethylformamide (DMF) in the second stage. The reaction was conducted for 16 hours. The obtained results are presented in table 1.

Table 1.

Effect of temperature on the yield of 4,6-diamino-2-mercaptopyrimidine reactions with alkyl halides

№	Reagents	Yield of product (% and temprature					Solvent
		20 °C	40° C	50° C	60°C	70°C	
1	DAMP, NaOH, Butyl bromide	60	66	70	-	-	DMF
2	DAMP, NaOH, pentyl bromide	58	62	68	-	-	DMF
3	DAMP, NaOH, hexcyl bromide	55	59	64	-	-	DMF
4	DAMP, NaOH, heptyl bromide	52	57	62	68	74	DMF
5	DAMP, NaOH, nonyl bromide	40	45	51	63	71	DMF

As can be seen from this table, at 20°C, as the alkyl chain length increases, the reactivity decreases in the following order:

***n*-C_4H_9- < *n*-C_5H_{11}- < *n*-C_6H_{13}- < *n*-C_7H_{15}- < *n*-C_9H_{19}-**

This can be explained as follows: Although alkyl groups are not strong electron-withdrawing groups, as the chain length increases, a slight inductive effect arises, which slightly decreases the electrophilicity of the carbon attached to the halogen. However, this effect is less noticeable compared to steric hindrance. As the chain length increases (e.g., *n*-C_4H_9- < *n*-C_5H_{11}- < *n*-C_6H_{13}- < *n*-C_7H_{15}- < *n*-C_9H_{19}-), the steric hindrance around the electrophilic carbon increases. This makes it more difficult for the nucleophile to approach the carbon, slowing down the reaction.

Longer alkyl chain compounds are hydrophobic and dissolve worse in polar solvents (such as DMF or DMSO). The poor solubility of halides in the solvent reduces their concentration, which in turn decreases the reaction rate.

Table 2.

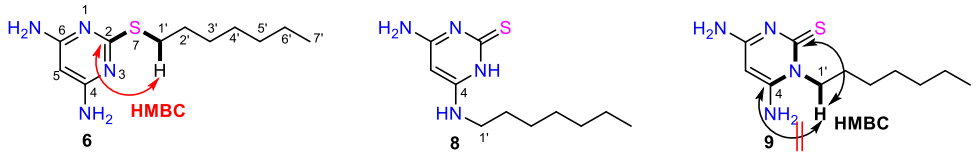
Yields and physicochemical properties of products obtained from the reaction of 4,6-diamino-2-mercaptopyrimidine with alkyl halides

Obtained product	Molar ratio of reagents	Yied of product %	R_f value	T_{liquid} °C
3	1:1,2	70	0,62	91-92
4	1:1,2	68	0,62	92-93
5	1:1,2	64	0,62	80-81
6	1:1,2	**74**	0,62	-
7	1:1,2	71	0,62	-

The results show that when DAMP is reacted with alkyl halides in a 1:1,2 mol ratio using methanol and DMF as solvents, *S*-alkyl products – thioesters are formed due to the SH group.

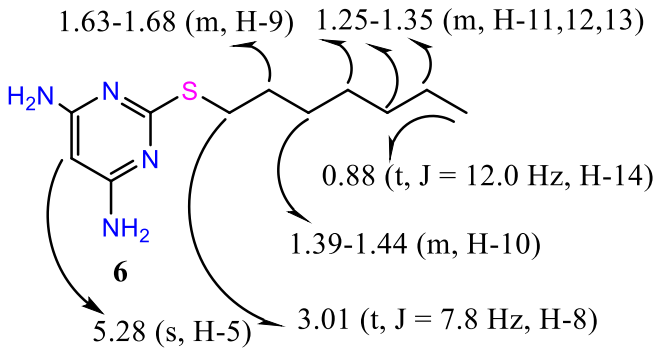
The individuality of the synthesized compounds was confirmed using TLC. A methanol:chloroform (1:5) system was chosen for TLC, and the R_f values of the synthesized compounds were determined.

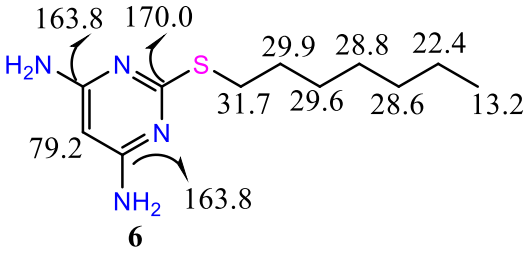
In the monoalkylation process, three products may be formed (**6**, **8**, and **9**).



Therefore, the structure of the products (**3**-**7**) was studied in detail using comprehensive spectroscopic analysis.

In the ^{1}H NMR spectrum of compound **6**, a triplet signal for the terminal methyl group (H7') of the heptyl chain was observed at δ 0.87 ppm. The ten methylene protons belonging to the *n*-heptyl group (H2'–H6') gave signals in the δ 1.22–1.32, 1.36–1.41, and 1.60–1.65 ppm ranges. The two methylene protons (H1') close to the sulfur atom appeared as a triplet at δ 3.01 ppm. The singlet signal at δ 5.26 ppm corresponded to the aromatic proton (H5) in the pyrimidine ring.





Analysis of the ^{1}H and ^{13}C NMR spectra of compound **6.**

In the ^{13}C NMR spectrum, the terminal methyl carbon (C7') was observed at δ 13.2 ppm, while the methylene carbons (C2'–C6') gave signals in the δ 22.4–29.9 ppm range, corresponding to the aliphatic group. The carbon (C1') adjacent to the sulfur atom showed a chemical shift at δ 31.7 ppm, which is characteristic of *S*-alkylation. If an *N*-alkylated product had been formed, according to the literature, the N-CH_2 signal should have appeared at approximately δ 43 ppm. The aromatic carbons were observed at δ 79.2 ppm (C5), δ 163.8 ppm, and δ 170.0 ppm (C2).

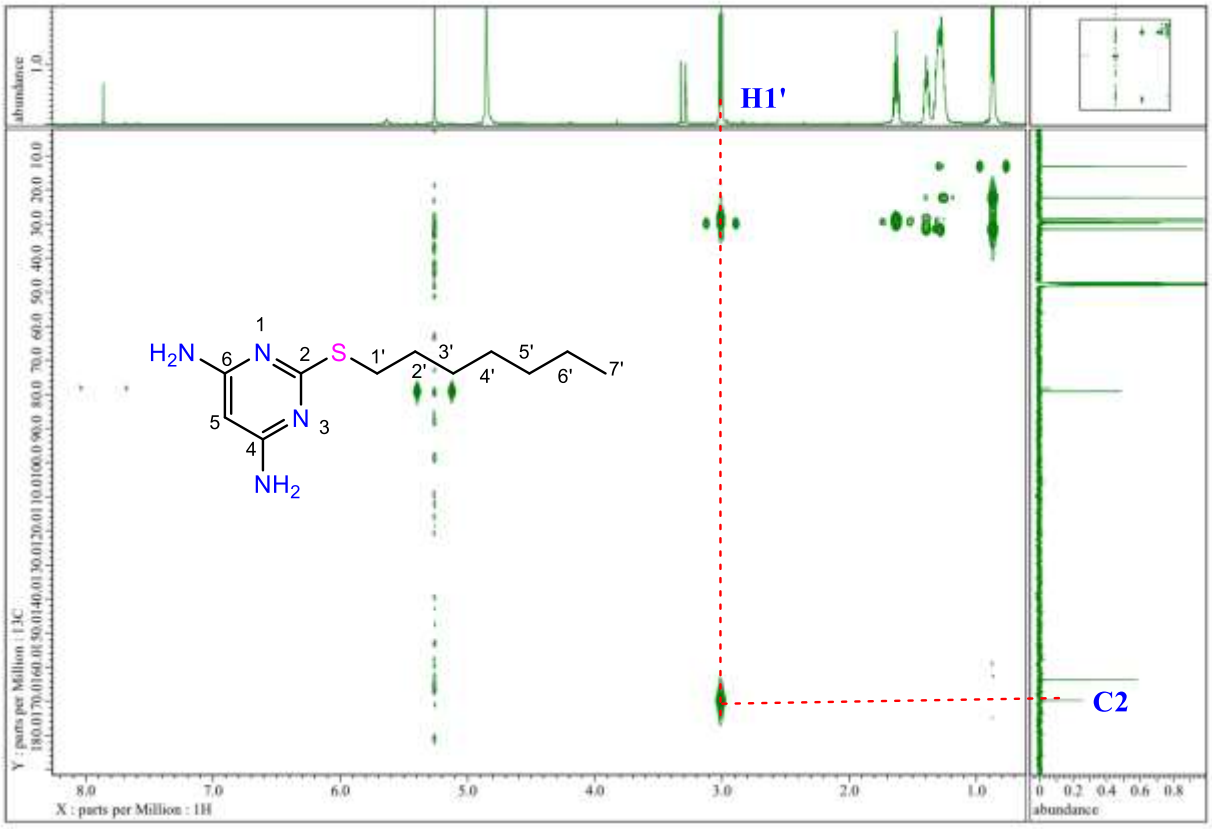


Figure 1. HMBC NMR spectra of compound **6**.

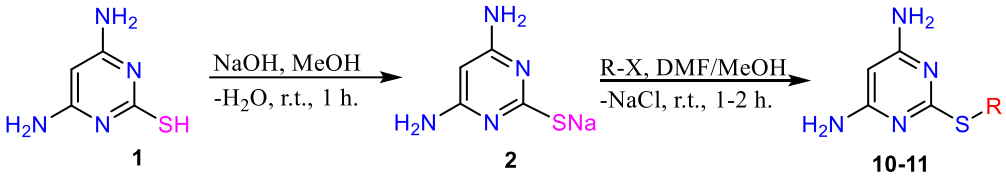
Attention was given to precisely identifying the alkylation site using HMBC analysis. A careful examination of the HMBC spectrum revealed key cross-peaks, with the most significant ^{4}JCH cross-correlation observed between H1' and C2. This confirmed that the alkyl group is bonded to the sulfur atom, aligning with the structure of compound **6**. The structure of compound **6** was reliably confirmed

based on the above spectroscopic data. In the HMBC spectrum, a significant correlation between H1' and C2 was observed (compound **6**). In contrast, for the possible formation of *N*-alkylated products (**8** and **9**), a correlation between H1' and C4 should have been observed in the HMBC spectrum. However, no such correlation was detected in the HMBC analysis. While it is known that the absence of a correlation in the NMR analysis of organic compounds does not necessarily provide a definitive conclusion, we used this indirect evidence to make a better assumption (Figure 1).

This selectivity can be explained by the "hard and soft acid and base" (HSAB) theory. According to this theory, soft bases (such as sulfur anions) are more likely to react with soft acids (such as alkyl halides).

Alkylation reaction of 4,6-diamino-2-mercaptopyrimidine with allyl and propargyl bromides

The synthesis of *S*-alkyl derivatives based on DAMP and unsaturated alkyl halides was studied. According to the research results, when the reactions of DAMP with unsaturated alkyl halides were conducted in aprotic solvent under basic conditions, a significant increase in reaction rate and product yield was observed.



Here: R = allyl (**10**), propargyl (**11**).

To study this process, *S*-alkylation reactions between DAMP and unsaturated alkyl bromides were carried out. Initially, DAMP and NaOH were dissolved in methanol and stirred for 1 hour using a magnetic stirrer. During this stage, the sodium salt of DAMP was formed, and then methanol was completely evaporated using a rotary evaporator.

Table 3.

Effect of solvent, reaction duration, and initial reagent ratio on the reaction yield of 4,6-diamino-2-mercaptopyrimidine with allyl and propargyl bromides.

№	Solvent	Ratio	Time	Yield	Ratio	Time	Yield	Ratio	Time	Yield
10	MeOH	1:1	2	58	1:1,2	1,5	59	1:2	1	62
	DMF	1:1	2	86	1:1,2	1,5	87	1:2	1	89
11	MeOH	1:1	2	56	1:1,2	1,5	59	1:2	1	62
	DMF	1:1	2	85	1:1,2	1,5	87	1:2	1	90

In the next step, the resulting sodium salt of DAMP was dissolved in DMF. Then, allyl (or propargyl) bromide was added dropwise, and the mixture was

reacted for 1-2 hours with stirring. As a result, the formation of *S*-alkyl derivatives was observed.

For the reaction of DAMP with unsaturated allyl (propargyl) bromides, the most favorable condition was an alkaline environment, and the reaction yield could be improved by using aprotic solvent such as DMF.

Table 4.

Physical and chemical properties of products obtained from the reaction of 4,6-diamino-2-mercaptopyrimidine with allyl and propargyl bromides

Number of product	Yield of product %	T_l, °C	R_f methanol:chloroform 1:5	Colour of product
10	89	220,5-220,6	0,62	**Brown crystal**
11	90	119,9-120	0,61	**Brown crystal**

Table 3 shows the results of studying the effect of solvent, reaction duration, and initial reagent ratio on the reaction yield between the Na salt of DAMP and unsaturated alkyl bromides. The reaction was carried out at various molar ratios of 1:1, 1:1.2, and 1:2, and over different time intervals of 1 hour, 1.5 hours, and 2 hours. As a result, it was observed that the reaction yield increased with the molar ratio. The highest yield and the shortest reaction time (1 hour) were achieved at a 1:2 molar ratio.

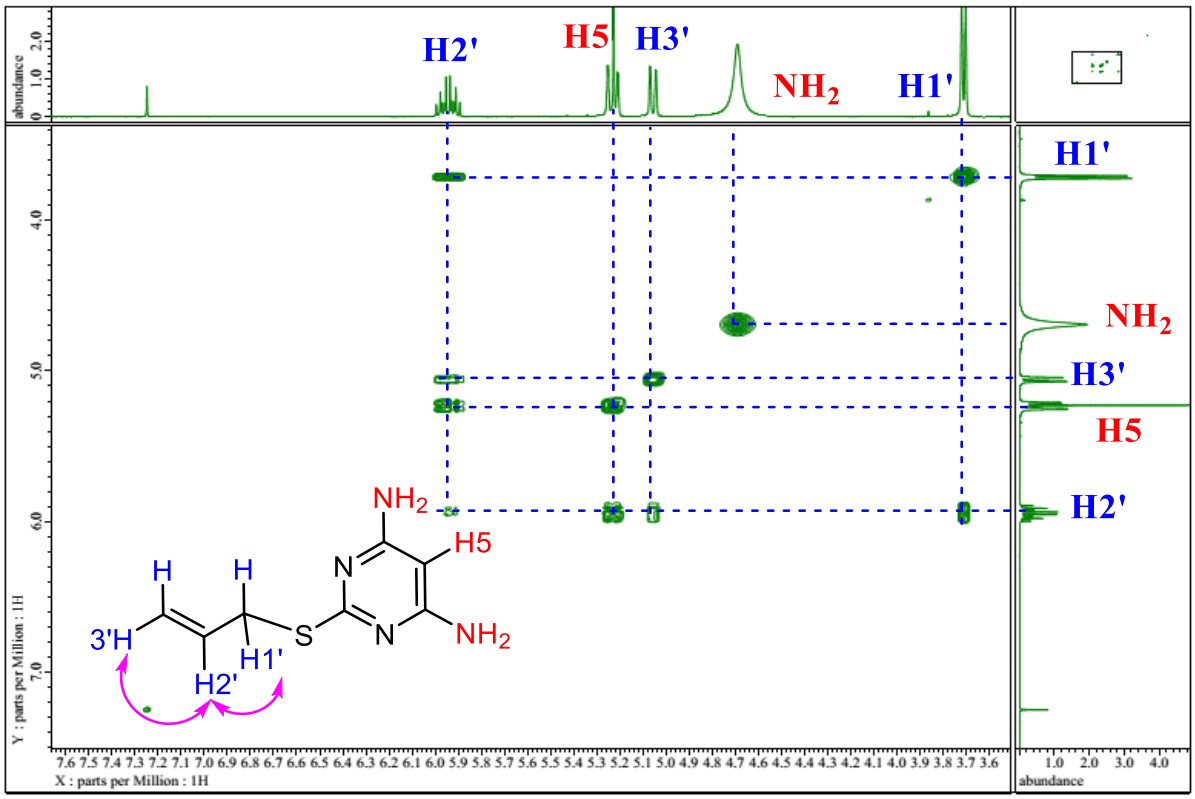


Figure 2. COSY NMR spectral analysis of compound **10**

The effect of the solvent on the reaction yield was also studied, using methanol and DMF. Methanol, as a polar protic solvent, showed an average yield. The ability of methanol to stabilize ionic intermediates or transition states helped

the reaction, but did not maximize the yield. DMF, as a polar aprotic solvent, provided a significantly higher yield than methanol. The polar nature of DMF effectively dissolved the initial reagents, enhancing the nucleophilicity of DAMP and ensuring the reaction proceeded quickly and with a high yield.

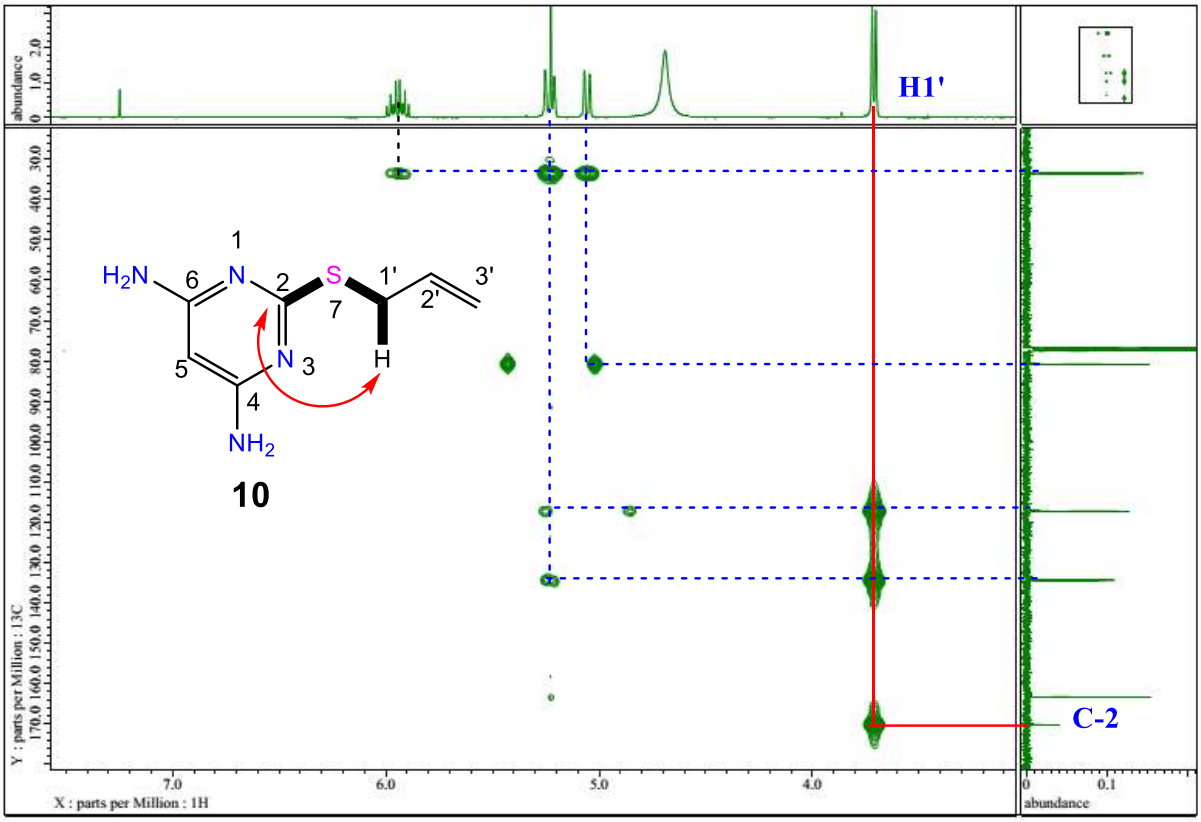


Figure 3. HMBC NMR spectral analysis of compound **10**

The COSY spectrum plays a crucial role in determining the structure of compound 10. This spectrum allows for the identification of proton-proton couplings and confirms the structure of the allyl chain.

In the COSY spectrum, the proton signal corresponding to the S-CH_2 group appears at δ 3.71 ppm, while the CH proton of the allyl group is located at δ 5.92 ppm. The presence of a cross-peak between these signals confirms that the S-CH_2 group is directly connected to the allyl chain. Cross-peaks observed between the terminal vinyl protons (CH_2) and the central allylic proton (CH) at δ 5.93 ppm and δ 5.21 ppm, respectively, further confirm the presence of vinyl and allylic linkages within the allyl chain. These observed correlations (cross-peaks) demonstrate the chain-like structure of the allyl group and illustrate the coupling characteristics of the vinyl protons. This confirms that the allyl group is attached to the pyrimidine ring via a sulfur atom as a result of the reaction (Figure 2).

The structure of the compound was confirmed using the HMBC method. This analysis helps identify the main long-range correlations between the allyl group and the pyrimidine ring and supports the connectivity of the molecule's structure. In the proton NMR spectrum, the doublet signal observed at 3.70 ppm

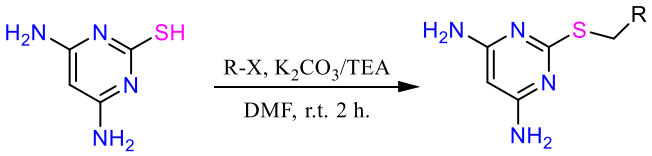
corresponds to the S-CH_2 methylene protons, showing a strong long-range correlation with the C-2 atom of the pyrimidine ring.

This observation confirms that the allyl group is connected to the sulfur (S) atom through the methylene group. Based on the HMBC data, the 13C signals of the pyrimidine ring and the allyl group were identified. The observed correlations include the following: the S-CH_2 methylene protons correlate with C-2 of the pyrimidine ring. The terminal vinyl protons (CH=CH_2) of the allyl group correlate with the methylene carbon (S-CH_2) and the central allyl carbon. The terminal vinyl protons of the allyl group show the expected long-range correlations with their adjacent methylene carbon and the sulfur-bound carbon. This confirms that the allyl group is attached to the sulfur atom. The protons corresponding to the NH_2 group (in the 4- and 6-positions) showed long-range correlations with the relevant carbons in the pyrimidine ring, confirming the positions of the substituent groups on the pyrimidine ring.

The HMBC data, particularly the strong correlation between the S-CH_2 doublet at 3.70 ppm and C-2, proves that the *S*-alkylation of DAMP with allyl bromide was successful. These results indicate that the reaction proceeded through sulfur (*S*) alkylation rather than nitrogen (*N*) alkylation (Figure 3).

The structure of the reaction products of DAMP with unsaturated alkyl halides was analyzed using IR, 1D, 2D NMR, LCMS, and HRMS spectroscopic methods.

The reactions of DAMP with benzyl halides were carried out at a 1:1, 1:1.2, and 1:1.5 molar ratio of reagents, at room temperature, under alkaline conditions, using DMF as the solvent. The following reaction equation led to the formation of the products.



1 **12-20**

Here, R-Benzyl (**12**), 4-methylbenzyl (**13**), 2,4-dimethylbenzyl (**14**), 2,5-dimethylbenzyl (**15**), 2,6-dimethylbenzyl (**16**), 3-chlorobenzyl (**17**), 4-chlorobenzyl (**18**), 2,4-dichlorobenzyl (**19**), and 2,6-difluorobenzyl (**20**).

DAMP contains two main nucleophilic centers: based on the above experiments, *S*-benzyl derivatives were obtained in high yields by reacting DAMP with benzyl halides at room temperature in a polar aprotic solvent. The results are presented in table 5.

As a result of the reaction of DAMP with benzyl halides at a 1:1,2 molar ratio, at room temperature in the presence of a solvent, it was observed that DAMP was completely consumed in the TLC, and *S*-benzyl products were formed due to the thiol group.

From the reaction of DAMP with exchanging benzyl halides at a 1:1,2 molar ratio, at room temperature in the presence of a polar aprotic organic solvent, the

following yields were obtained: **12** (85%), **13** (85%), **14** (90%), **15** (87%), **16** (82%), **17** (66%), and **18** (51%).

In this study, the yield of *S*-alkylated DAMP derivatives was analyzed. It was observed that the higher or lower yield depends on the electron-donor the substituents on the benzene ring.

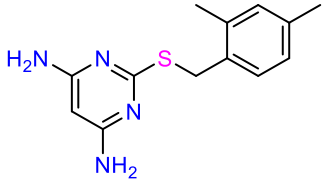
5-Table.

Effect of the ratio of initial reagents on the reaction yield of 4,6-diamino-2-mercaptopyrimidine with benzyl halides (DAMP:Benzyl halide:K2CO3/TEA)

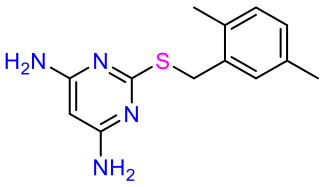
№	Benzyl halogens K_2CO_3/TEA	1:1:2 yield %	1:1,2:2 yield %	1:1,5:2 yield %	Reaction time (h)
14	2,4-dimethylbenzyl chloride	81	**90**	**90**	2
15	2,5-dimethylbenzyl chloride	78	87	87	2
16	2,6-dimethylbenzyl chloride	70	78	82	2

The results from the table show that as a result of DAMP's reaction with benzyl halides in a 1:1,2 molar ratio at room temperature in the presence of a solvent, complete consumption of DAMP was observed. S-benzyl products were formed due to the thiol group.

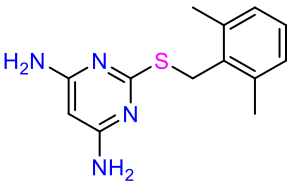
From the values presented in Table 5, it is evident that the reaction of DAMP with exchanging benzyl halides in a 1:1,2 molar ratio at room temperature in a polar aprotonic organic solvent leads to the formation of *S*-benzyl products.



14 (90%)



15 (87%)



16 (82%)

In the 2,4-dimethylbenzyl molecule, the methyl groups at the 2- and 4-positions increase the electron density of the carbon atoms located at the *ortho*- and *para*- positions relative to themselves. Due to the favorable orientation of the methyl groups at these positions, the electron deficiency at the benzylic carbon is significantly reduced, resulting in a highly stabilized 2,4-disubstituted benzyl carbocation. Therefore, the reaction proceeds rapidly via the S_N1 mechanism, as the transition state of the reaction depends on the formation of a stable carbocation. The faster and more stable the carbocation is formed, the faster the reaction proceeds.

In the 2,5-dimethylbenzyl molecule, the methyl group at the 2-position contributes to carbocation stabilization due to its favorable position relative to the benzylic carbon. However, the methyl group at the 5-position is located in the meta position relative to the benzylic group, and its electron-donating effect is negligible. As a result, only one methyl group contributes significantly to the stabilization of the benzylic group. Consequently, the reaction yield with 2,5-dimethylbenzyl halide is slightly lower compared to that with 2,4-dimethylbenzyl halide.

In the case of 2,6-dimethylbenzyl halide, although both methyl groups are electron-donating and are favorably oriented, their presence in the *ortho* positions creates steric hindrance for the bulky nucleophile DAMP (dimethylaminopyridine) with a sulfur nucleophile. This steric hindrance distorts the coplanarity of the molecule, reducing the effectiveness of the positive inductive effect of both alkyl groups on the benzylic position. As a result, the reaction proceeds via the S_N2 mechanism and shows a lower yield compared to the reactions with 2,4- and 2,5-disubstituted benzyl halides.

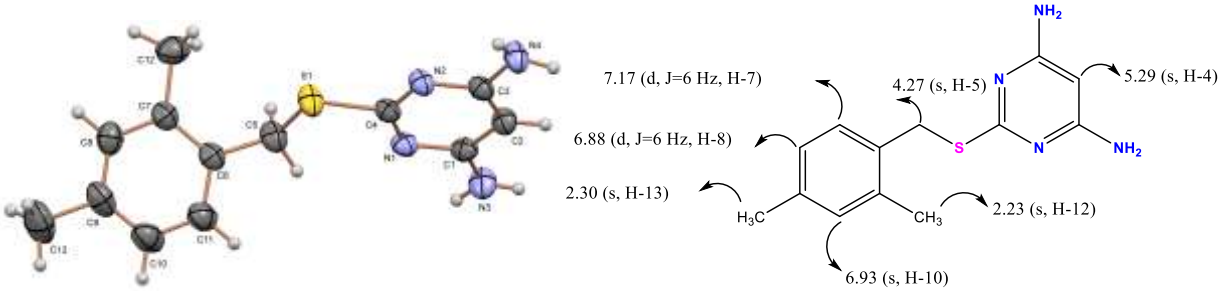


Figure 4. Crystal structure and ^{1}H NMR spectral analysis of compound **14**.

The individuality of the synthesized compounds was determined using TLC. For this, a methanol:chloroform (1:5) system was chosen, and the R_f values of the synthesized compounds were determined. The structures of the synthesized *S*-benzyl derivatives were confirmed by IR, NMR, ^{1}H, ^{13}C, HMBC, X-ray crystallographic analysis, and mass spectrometry.

Study of *S*-alkyl acetoester derivatives of 4,6-diamino-2-mercaptopyrimidine

In the synthesis of *S*-alkyl acetoester derivatives, the high nucleophilicity of DAMP was taken into account. The reaction was carried out with methyl and ethyl esters of monochloroacetic acid in a DMF solvent at 50 °C for two hours. The methyl derivative was obtained with a 75% yield, while the ethyl derivative was synthesized with a 67% yield.

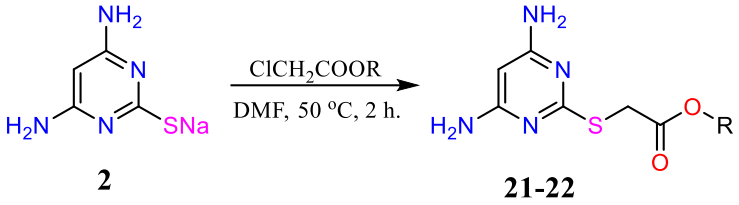
Table 6.

Yields of *S*-alkyl acetoester derivatives obtained as a result of the reaction

№	Yield of product %	R_f MeOH:$CHCl_3$ 1:5	Ratio of reagents	Reaction time	Colour compound
21	75	0,62	1:1	2	Brown
22	67	0,62	1:1	2	Brown
23	66	0,62	1:1:1,2	4	Brown
24	61	0,62	1:1:1,2	4	Brown
25	85	0,62	1:1:1,2	4	Brown
26	82	0,62	1:1:1,2	4	Light yellow
27	80	0,62	1:1:1,2	4	Light yellow

This difference can be explained by steric hindrance and electronic effects. The smaller methyl group makes it easier to react with the electrophilic center

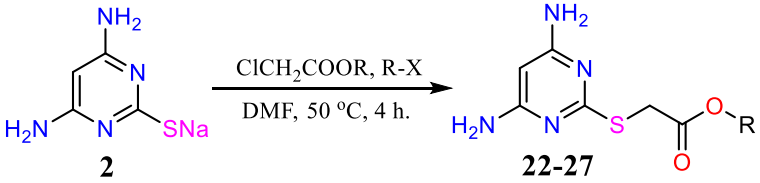
(chloroacetic acid ester). In contrast, the ethyl group, being slightly larger, exerts more steric effects, reducing the ability of the thiolate ion to attack the electrophile, resulting in a relatively lower yield. Additionally, the DMF solvent, being a polar aprotic solvent, increased the reactivity of the nucleophilic S^- ion and accelerated the *S*-alkylation reaction.



2 **21-22**

R = Me, Et

Additionally, a "*one-pot*" reaction of DAMP the sodium salt of monochloroacetic acid, and alkyl halides was performed. As a result, *S*-alkyl acetoester derivatives were synthesized.



2 **22-27**

R = allyl (**23**), propargyl (**24**), benzyl (**25**) 2,4-dimethylbenzyl (**26**), 2,5-dimethylbenzyl (**27**); X = Br, Cl.

Chapter 3 of the dissertation, titled "**Biological properties of synthesized compounds**," presents the results of the study on the antibacterial activity, anticancer activity, and insecticidal activity of the compounds obtained.

Antibacterial Activity

Compound **15** exhibited antibacterial activity against various gram-positive and gram-negative bacteria. The biological activity of this compound is related to the structure of the bacterial cell wall and membrane permeability. Gram-positive bacteria, with their strong murein layer, showed a higher sensitivity to compound **15**. *S. aureus* exhibited greater sensitivity compared to *B. subtilis* (18 mm vs. 16 mm), indicating that compound **15** has a stronger effect on the membrane structure of *S. aureus*.

Table 7.

Antibacterial activity of 2-{(2,5-dimethylbenzyl)thio}pyrimidine-4,6-diamine

№	**Gram-positive bacteria**		**Gram-negative bacteria**		***Candida albicans***
	Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	
15	16 mm	18 mm	20 mm	17 mm	15 mm

Gram-negative bacteria are protected by an outer membrane, making them more resistant to the effects of antibiotics and other chemicals. However, compound **15** showed the highest antibacterial activity against *E. coli* with a 20 mm inhibition zone, while *P. aeruginosa* was slightly less sensitive, with a 17 mm

inhibition zone recorded. *Candida albicans* (15 mm) also showed sensitivity to compound 15. This result indicates that compound 15 also possesses antifungal activity, although its effect on bacteria is slightly higher. Thus, compound **15** demonstrated the highest antibacterial activity against *Escherichia coli* (20 mm), followed by *S. aureus* (18 mm), *P. aeruginosa* (17 mm), *B. subtilis* (16 mm), and *C. albicans* (15 mm).

Anticancer Activity

Cancer is one of the leading causes of death worldwide. The highest mortality rates due to cancer are associated with stomach, liver, cervical, breast, prostate, lung, and colorectal cancers. It is known that 2-thiopyrimidine compounds exhibit anticancer biological activities.

All analyzed compounds (**10**, **11**, **14**, **15**, **24**, **25**) showed varying degrees of cytotoxic activity against the HeLa cell line. The degree of cell death was dependent on their concentration, with maximal cytotoxic effects observed at higher concentrations (100 μg/ml) (Table 8).

The highest antiproliferative activity was exhibited by compound **15**, with a cytotoxic effect of 95.76% at a concentration of 100 μg/ml. At concentrations of 10 and 1 μg/ml, the degree of inhibition of cell growth decreased to 20.05% and 15.01%, respectively. This indicates that its cytotoxic effect is concentration-dependent.

Additionally, compound **14** also demonstrated high cytotoxicity, inhibiting cell growth by 44.77% at a concentration of 100 μg/ml. Compound **25** showed a cytotoxic effect of 32.10% at 100 μg/ml, which, although slightly lower than compound **24**, still indicated a significant antiproliferative effect.

The positive control agents used in the study—cisplatin and doxorubicin—also showed cytotoxic activity. Cisplatin inhibited 88.93% of cells at a concentration of 100 μg/ml, confirming its efficacy as a cytotoxic agent. Doxorubicin, on the other hand, demonstrated a cytotoxic effect of 70.36%, which is slightly lower than the results obtained with some of the tested compounds.

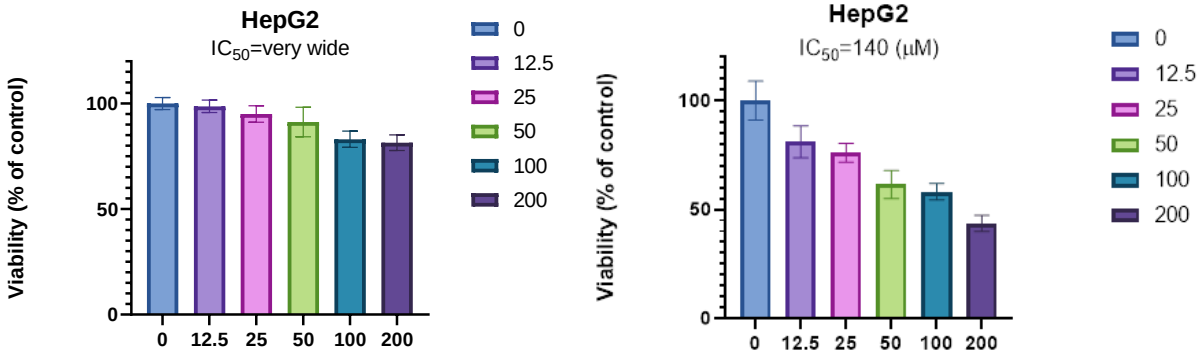
Table 8.

The degree of inhibition of HeLa cells by 4,6-diamino-*S*-alkylthiopyrimidine derivatives is dependent on their concentration

№	Mkg/ml / Samples	Live cells			Inhibition		
		100	10	1	100	10	1
1.	**10**	86,96	98,15	97,91	13,04	1,85	2,09
2.	**11**	94,96	97,05	98,28	5,04	2,95	1,72
3.	**14**	55,23	71,09	74,78	44,77	28,91	25,22
4.	**15**	4,42	79,95	84,99	95,76	20,05	15,01
5.	**26**	67,90	80,57	83,52	32,10	19,43	16,48
6.	**27**	80,44	84,50	87,21	19,56	15,50	12,79
7.	Cisplatin	11,07	85,49	104,43	88,93	14,51	4,18
8.	Doxorubicin	29,64	79,09	90,28	70,36	20,91	9,72

As a result, some *S*-alkylated DAMP derivatives demonstrated significant cytotoxicity against HeLa cells. In particular, compounds **15** and **14** show potential as promising cytotoxic agents.

4,6-Diamino-mercaptopyrimidine-*S*-benzyl derivatives' antiproliferative activity against HepG2 liver cancer cell line: For HepG2 cells, compound **14** did not show an IC_{50} value in the selected concentration range, and the expected value was too broad to be recorded. However, a tendency of decreased cell viability was observed: as the concentration of compound **14** increased, cell viability decreased proportionally. For example, at a concentration of 50 µM, cell viability decreased by 10%, and at 200 µM, a decrease of 20% was observed.



24h treatment of compound **14** 24h treatment of compound **15**

Figure 4. Cytotoxic effect of compounds **14** and **15** on the HepG2 human liver cancer cell line.

On the other hand, compound **15** exhibited cytotoxic activity. At a concentration of 12.5 µM, cell viability remained around 80%, but as the concentration increased, cell viability decreased. At 200 µM, the viable cells were around 40%, and the IC_{50} was found to be 140 µM. This indicates that compound **15** has higher cytotoxic activity in HepG2 cells compared to compound **14**. Compound **14** is relatively less toxic, while compound **15** exhibited moderate cytotoxicity. Therefore, it is necessary to further investigate the anticancer potential of compound **15**, including evaluating its ability to induce apoptosis or necrosis.

Insecticidal Activity

To assess the insecticidal activity of DAMP's *S*-alkyl derivatives, *Helicoverpa zea* and *Spodoptera frugiperda* cell lines were used. The compounds were applied to the cells at concentrations of 10 and 100 µM/ml, and their insecticidal activity was evaluated using the MTT assay.

Upon analysis of the obtained results, it was found that various compounds exhibited different levels of insecticidal activity. One of the most effective compounds was compound **26**, which demonstrated high activity against *Spodoptera frugiperda* cells. Compound **6** also showed activity in *Spodoptera frugiperda* cells and exhibited 65% activity at 10 µM/ml and 70.1% activity at 100

μM/ml in *Helicoverpa zea* cells. Compound 7 did not show insecticidal activity in *Spodoptera frugiperda* cells (0%).

Table 10.

Insecticidal activity of 4,6-Diamino-S-alkylthiopyrimidine derivatives

№	***Helicopvera zea***		***Spodotera frugiperda***	
	10 mkM/ml	100 mkM/ml	10 mkM/ml	100 mkM/ml
6	65 %	70,1 %	72.7 %	88,2 %
7	29,65 %	38.1 %	0 %	0%
12	42,9%	43,8%	82 %	85%
14	51,7 %	61,03%	85 %	61 %
15	9,5%	19%	14%	24 %
26	26,9%	72,9%	83 %	67%
27	0 %	54,7%	25 %	36.7%
"*Bagira*" 20%	**79,3%**	**89,6%**	**81.5 %**	**91.3%**

As a control, the "*Bagira*" 20% insecticide showed high efficiency in both cell lines and was used as a comparison standard for the test compounds.

These findings provide a scientific basis for identifying effective compounds against insects and selecting promising compounds for future use as insecticides.

Chapter Four of the dissertation contains the experimental section, including the chemical modification of the compounds and the synthesis methods. The identification and structural determination methods of the compounds, such as chromatography (LCMS, HRMS, TLC), spectroscopy (IR-, ^{1}H- and ^{13}C-NMR) results, are also provided.

Conclusions

1. For the first time, new derivatives of DAMP (4,6-diamino-2-mercaptopyrimidine) containing propargyl, heptyl, nonyl, 4-methylbenzyl, 2,4-dimethylbenzyl, 2,5-dimethylbenzyl, 2,6-dimethylbenzyl, 2,6-difluorobenzyl, 2,4-dichlorobenzyl, 3-chlorobenzyl, and 4-chlorobenzyl substituents were synthesized. The influence of various factors on product yield was determined, and the reaction conditions were optimized.
2. Novel thioalkyl acetoester derivatives of DAMP bearing methyl, ethyl (in a one-pot method), allyl, propargyl, benzyl, 2,4-dimethylbenzyl, and 2,5-dimethylbenzyl radicals were synthesized. Optimal conditions were established, and the structures were confirmed using modern physicochemical methods.
3. In S-alkyl derivatives, an increase in the chain length led to a decrease in reaction yield. When the temperature was increased from 20 °C to 70 °C, the yield improved. For butyl, pentyl, and hexyl derivatives, mono-products were obtained optimally at 50 °C, while for heptyl and nonyl derivatives, the optimal temperature was 70 °C.
4. The synthesis of allyl and propargyl derivatives of DAMP was carried out in both protic and aprotic solvents. It was determined that the reaction yield was higher in aprotic solvents. When the molar ratio of DAMP sodium salt to allyl/propargyl bromide was 1:2, both the reaction rate and yield (90%) increased significantly.

5. Based on the reactions involving DAMP, the nucleophilic substitution reactivity of dimethylbenzyl chlorides bearing electron-donating substituents was investigated. The reactivity trend was found to decrease in the order: 2,4-dimethylbenzyl chloride > 2,5-dimethylbenzyl chloride > 2,6-dimethylbenzyl chloride. This showed that both steric and electronic effects of the substituents significantly influence the reaction course.
6. The 2,5-dimethylbenzyl-substituted derivative of DAMP exhibited higher antibacterial activity against gram-negative bacteria (Escherichia coli, 20 mm) than against gram-positive bacteria. The S-benzyl derivatives showed low cytotoxicity against HepG2 cells (IC_{50} = 140 μM), while demonstrating high cytotoxic activity against HeLa human cancer cells (4.42 μM), surpassing the effectiveness of cisplatin, a commonly used chemotherapeutic drug. In addition, among *S*-alkyl derivatives tested for insecticidal properties, the heptyl derivative exhibited the highest insecticidal activity (70%) against the maize weevil (*Sitophilus zeamais*).

НАУЧНЫЙ СОВЕТ DSc.03/30.12.2019.K.01.03 ПО ПРИСУЖДЕНИЮ УЧЁНОЙ СТЕПЕНИ ДОКТОРА НАУК ПРИ НАЦИОНАЛЬНОМ УНИВЕРСИТЕТЕ УЗБЕКИСТАНА

НАЦИОНАЛЬНЫЙ УНИВЕРСИТЕТ УЗБЕКИСТАНА

САЛИЕВА ГУЛРУХ БАХОДИРОВНА

СИНТЕЗ *S*-АЛКИЛЬНЫХ ПРОДУКТОВ НА ОСНОВЕ 4,6-ДИАМИНО-2-МЕРКАПТОПИРИМИДИНА И ИХ БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ

02.00.03 — Органическая химия (химические науки)

АВТОРЕФЕРАТ ДИССЕРТАЦИИ ДОКТОРА ФИЛОСОФИИ (PhD) ПО ХИМИЧЕСКАМ НАУКАМ

Ташкент–2025

Тема диссертации доктора философии (PhD) зарегистрирована в Высшей аттестационной комиссии при Министерстве высшего образования, науки и инноваций Республики Узбекистан за номером B2024.4PhD/K622.

Диссертация выполнена в Национальном университете Узбекистана.

Автореферат диссертации на трех языках (узбекский, английский, русский) размещен на веб-странице по адресу www.ik-kimyo.nuu.uz и информационно-образовательном портале «ZiyoNET» по адресу www.ziyonet.uz.

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Ведущая организация:	**Ташкент фармацевтический институт**

Защита диссертации состоится «05» июня 2025 г.в 9⁰⁰ часов на заседании Научного совета 03/30.12.2019.K.01.03 при Национальном университете Узбекистана. (Адрес: 100174, Ташкент, ул. Университетская 4, тел.: (99871) 227-12-24; факс: (99824) 246-53-21; 246-02-24. e-mail: ilmiy_kengash@nuu.uz).

Докторская диссертация зарегистрирована в Информационно-ресурсном центре Национального университета Узбекистана за №, с которой можно ознакомиться в ИРЦ. (100174, Ташкент, ВУЗ городок, Фундаментальная библиотека НУУз. Тел.: (99871) 246-67-71).

Автореферат диссертации разослан «22» 05 2025 года.

(протокол рассылки №3 от 21. 05 2025 года).

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ВВЕДЕНИЕ (аннотация докторской (PhD) диссертации)

Целью исследования Она заключается в синтезе *S*-алкильных производных на основе 4,6-диамино-2-меркаптопиримидина и исследовании их биологической активности.

Объекты исследования. 4,6-диамино-2-меркаптопиримидин (ДАМП), *S*-натриевая соль ДАМПа, а также его *S*-алкильные производные: *n*-бутил-, *n*-пентил-, *n*-гексил-, *n*-гептил-, *n*-нонил-, аллил-, пропаргил-, бензил-, 4-метилбензил-, 2,4-диметилбензил-, 2,5-диметилбензил-, 2,6-диметилбензил-, 3-хлорбензил-, 4-хлорбензил-, 2,4-дихлорбензил-, 2,6-дифторбензил-. Также объектами исследования являются 2-тиоалкилацетоэфирные производные ДАМП с метил-, этил-, аллил-, пропаргил-, бензил-, 2,4-диметилбензил-, 2,5-диметилбензил- радикалами.

Научная новизна исследования заключается в следующем:

впервые были синтезированы производные ДАМП с радикалами: *n*-гептил-, *n*-нонил-, аллил-, пропаргил-, 4-метилбензил-, 2,4-диметилбензил-, 2,5-диметилбензил-, 2,6-диметилбензил-, 3-хлорбензил-, 4-хлорбензил-, 2,4-дихлорбензил-, 2,6-дифторбензил-;

впервые методом «*one pot*» были получены тиоалкилацетоэфирные производные ДАМП с радикалами: аллил-, пропаргил-, бензил-, 2,4-диметилбензил-, 2,5-диметилбензил-;

установлено, что при увеличении длины алкильной цепи в *S*-алкильных производных выход реакции снижается, а с повышением температуры от 20 до 70 °C выход увеличивается, для бутил-, *n*-пентил-, *n*-гексилпроизводных оптимальная температура — 50 °C, для *n*-гептил- и *n*-ноннилпроизводных — 70 °C, при этом образуются преимущественно мономолекулярные продукты;

при синтезе аллильных и пропаргильных производных ДАМП в протонных и апротонных растворителях установлено, что выход реакции выше в апротонных средах. При соотношении натриевой соли ДАМП и аллил- или пропаргилбромидов 1:2 достигается высокая скорость реакции и выход до 90%;

Установлено, что способность диметилзамещённых бензильных производных, содержащих электронодонорные заместители, вступать в реакции нуклеофильного замещения с ДАМП уменьшается в следующем порядке: 2,4-диметилбензил хлорид > 2,5-диметилбензил хлорид > 2,6-диметилбензил хлорид;

структура *S*-алкильных производных, полученных на основе ДАМП, была подтверждена с помощью масс-спектрометрии, ЯМР, ИК-спектроскопии и рентгеноструктурного анализа.

S-бензильное производное (соединение **15** 4,42 мкМ) проявило в 2,5 раза более высокую активность против клеток рака шейки матки (HeLa), чем эталонный препарат «цисплатин» (11,07 мкМ), уничтожив 95,8% живых клеток.

Внедрение результатов исследования.

Результаты рентгеноструктурного анализа (РСА) 2-{(2,4-диметилбензил)тио}пиримидин-4,6-диамина были внесены в базу данных Кембриджского кристаллографического центра (Cambridge crystallographic data centre) под регистрационным номером 2431935 от 25 марта 2025 года. Это позволило определить структуру новых соединений, входящих в состав алкилзамещённых тиопиримидинов.

Полученные результаты были использованы в рамках выполнения фундаментального проекта «Ограничение пролиферации раковых клеток за счёт блокирования аквапориновых каналов с помощью биологически активных соединений: экспериментальные исследования на молекулярном уровне» (2022–2024 гг.), реализуемого в научной лаборатории «Инновационные фармацевтические соединения» Ташкентского фармацевтического института (справка Министерства высшего образования, науки и инноваций № 03/17-668 от 14 марта 2025 года). В результате было установлено, что синтезированные на основе 4,6-диамино-2-меркаптопиримидина *S*-алкилпроизводные проявляют ингибирующую активность в отношении клеток рака печени (HepG2).

Структура и объем диссертации. Диссертация состоит из введения, 4 глав, заключения, списка использованной литературы и приложений. Объем диссертации составляет 120 страниц.

E’LON QILINGAN ISHLAR RO‘YXATI
СПИСОК ОПУБЛИКОВАННЫХ РАБОТ
LIST OF PUBLISHED WORKS

I bo‘lim (I часть; I part)

1. Salieva G.B., Kenjaboev U.Z., Kholikov T.C., Matchonov A.D. Synthesis *S*-alkyl derivatives of 4,6-diaminopyrimidine-2-thiol // O‘zbekiston Milliy universiteti xabarlari. – T., 2024. T. 3. – № 1. – P. 430-432.
2. Salieva G.B., Tojimukhamedov H.C., Kholikov T.S. and A.D.Matchanov. Synthesis and spectroscopic analysis of 2-(allylthio) pyrimidine-4,6-diamine // O‘zbekiston Respublikasi FA ma’ruzalari. – T., 2024. – №. 5. – B. 49-53.
3. Salieva G., Turlibekov M., Kholikov T., Matchanov A. Reactions of 4,6-diamino-2-mercaptopyrimidine with monochloroacetic acid ethers // Journal of Universum, 2025. – № 2 (128). – P. 43-46.
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5. Salieva G., Kholikov T., Okmanov R.Y., Matchanov A., Khodjaniyazov K.U., Kadirova S., Torambetov B. Synthesis, crystal structure and Hirshfeld surface analysis of 2- [(2, 4-dimethylbenzyl) sulfanyl] pyrimidine-4, 6-diamine // Structure Reports, 2025. T. 81. – №. 4 (Q3).

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6. Salieva G.B., Kholikov T.C., Matchonov A.D. Synthesis *S*-benzyl derivative of 4,6-diaminopyrimidine-2-thiol// “Zamonaviy organik kimyo: Yutuqlar muammolar, yechimlar” mavzusidagi xorijiy olimlar ishtirokidagi ilmiy-amaliy konferensiya. – Toshkent, 2024. 20-21-sentyabr. – B. 44-45.
7. Salieva G.B., Kholikov T.C., Matchonov A.D. Synthesis S-alkyl derivatives of 4,6-diaminopyrimidine-2-thiol / “Kimyoning dolzarb muammolari” mavzusidagi Respublika ilmiy-amaliy konfrensiyasi. – Urganch, 2024. 21-22-iyun. – B. 456-459.
8. Salieva G.B., Kholikov T.C., Matchonov A.D. Synthesis unsaturated derivative of pyrimidine-4,6-diamine / “Kolloid kimyo: kimyoviy texnologiya, ekologiya va sanoat uchun innovatsiyalar va yechimlar” mavzusidagi Xalqaro ilmiy-texnikaviy anjuman. – T., 2025. 7-8-fevral. – B. 439-442.
9. Salieva G.B., Kholikov T.C., Matchonov A.D. Synthesis of methyl 2-{(4,6-diamino)pyrimidin-2-yl)thio}acetate / “Kolloid kimyo: kimyoviy texnologiya, ekologiya va sanoat uchun innovatsiyalar va yechimlar” mavzusidagi Xalqaro ilmiy-texnikaviy anjuman. – T., 2025. 7-8-fevral. – B. 436-439.