ISSN 2518-1483 (Online),
ISSN 2224-5227 (Print)

ACADEMIC JOURNAL OF PHYSICAL AND CHEMICAL SCIENCES

№2
2026

ISSN 2518-1483 (Online),
ISSN 2224-5227 (Print)

2026 • 2

CENTRAL ASIAN ACADEMIC
RESEARCH CENTER

ACADEMIC JOURNAL OF PHYSICAL AND CHEMICAL SCIENCES

PUBLISHED SINCE JANUARY 1944

ALMATY, NAS RK

ACADEMIC JOURNALOF PHYSICAL AND
CHEMICAL SCIENCES

2026 • 2

Editor-in-Chief:

ZHURINOV Murat Zhurinovich, Doctor of Chemical Sciences, Professor, Academician of IAAS and NAS RK, General Director of the Research Institute of Petroleum Refining and Petrochemicals (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=6602177960 https://www.webofscience.com/wos/author/record/2017489

Editorial Board:

KALIMOLDAYEV Maksat Nuradilovich, Doctor of Physical and Mathematical Sciences, Professor, Academician of NAS RK (Almaty, Kazakhstan), https://www.scopus.com/authid/detail uri?authorId=56153126500, https://www.webofscience.com/wos/author/record/2428551

ADEKENOV Sergazy Mynzhasarovich, Doctor of Chemical Sciences, Professor, Academician of NAS RK, Director of the JSC "Phytochemistry Research and Production Center", (Karaganda, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=7006153118, https://www.webofscience.com/wos/author/record/48648658

RAMAZANOV Tlekkabul Sabitovich, (Deputy Editor-in-Chief), Doctor of Physical and Mathematical Sciences, Professor, Academician of NAS RK (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=6701328029, https://www.webofscience.com/wos/author/record/13503476

ABIEV Rufat, Doctor of Technical Sciences (Biochemistry), Professor, Head of the Department of Optimization of Chemical and Biotechnological Equipment, St. Petersburg State Technological Institute (St. Petersburg, Russia), https://www.scopus.com/authid/detail.uri?authorId=6602431781, https://www.webofscience.com/wos/author/record/1405661

OLIVIERO Rossi Cesare, PhD (Chemistry), Professor at the University of Calabria (Calabria, Italy), https://www.scopus.com/authid/detail.uri?authorId=57221375979, https://www.webofscience.com/wos/author/record/399768

TIGINYANU Ion Mihailovich, Doctor of Physical and Mathematical Sciences, Academician, President of the Academy of Sciences of Moldova, Technical University of Moldova (Chisinau, Moldova), https://www.scopus.com/authid/detail.uri?authorId=7006315935, https://www.webofscience.com/wos/author/record/524462

SANG SU Kwak, PhD (Biochemistry, Agricultural Chemistry), Professor, Chief Scientist, Research Center for Plant Systems Engineering, Korea Research Institute of Bioscience and Biotechnology (KRIBB), (Daecheon, Korea), https://www.scopus.com/authid/detail.uri?authorId=59286321700, https://www.webofscience.com/wos/author/record/30028581

BERSIMBAYEV Rakhmetkazhi Iskenderovich, Doctor of Biological Sciences, Professor, Academician of NAS RK, L.N. Gumilyov Eurasian National University (Astana, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=7004012398, https://www.webofscience.com/wos/author/record/19854255

CALANDRA Pietro, PhD (Physics), Professor, Institute for the Study of Nanostructured Materials (Rome, Italy), https://www.scopus.com/authid/detail.uri?authorId=7004303066, https://www.webofscience.com/wos/author/record/616360

BOSHKAEV Kuantai Avgazyevich, PhD, Associate Professor, Department of Theoretical and Nuclear Physics, Al-Farabi Kazakh National University (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=54883880400, https://www.webofscience.com/wos/author/record/2080231

BURKITBAEV Mukhambetkali, Doctor of Chemical Sciences, Professor, Academician of NAS RK, (Almaty, Kazakhstan) https://www.scopus.com/authid/detail.uri?authorId=8513885600, https://www.webofscience.com/wos/author/record/29017135

QUEVEDO Hernando, Professor, National Autonomous University of Mexico (UNAM), Institute of Nuclear Sciences (Mexico City, Mexico), https://www.scopus.com/authid/detail.uri?authorId=55989741100, https://www.webofscience.com/wos/author/record/30353742

ZHUSUPOV Marat Abzhanovich, Doctor of Physical and Mathematical Sciences, Professor of the Department of Theoretical and Nuclear Physics, Al-Farabi Kazakh National University (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=6602166928, https://www.webofscience.com/wos/author/record/566

KOVALEV Alexander Mikhailovich, Doctor of Physical and Mathematical Sciences, Academician of NAS of Ukraine, Institute of Applied Mathematics and Mechanics (Donetsk,Ukraine), https://www.scopus.com/authid/detail.uri?authorId=7202799321, https://www.webofscience.com/wos/author/record/65533963

TAKIBAEV Nurgali Zhabagaevich, Doctor of Physical and Mathematical Sciences, Professor, Academician of NAS RK, Al-Farabi Kazakh National University (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=24077239000, https://www.webofscience.com/wos/author/record/1671760

KHARIN Stanislav Nikolaevich, Doctor of Physical and Mathematical Sciences, Professor, Academician of NAS RK, Kazakh-British Technical University (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=6701353063, https://www.webofscience.com/wos/author/record/2023295

ABISHEV Medeu Erzhanovich, Doctor of Physical and Mathematical Sciences, Professor, Corresponding Member of NAS RK, (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=26530759900, https://www.webofscience.com/wos/author/record/1556025

ABILMAGZHANOV Arlan Zainutallaevich, PhD in Chemistry, First Deputy Director General of JSC “Institute of Fuel, Catalysis and Electrochemistry named after D.V. Sokolsky”, (Almaty, Kazakhstan), https://www.scopus.com/authid/detail.uri?authorId=57197468109, https://www.webofscience.com/wos/author/record/2024265

ACADEMIC JOURNAL OF PHYSICAL AND CHEMICAL SCIENCES.
ISSN 2518-1483 (Online), ISSN 2224-5227 (Print)
Owner: «Central Asian Academic Research Center» LLP (Almaty).
The certificate of registration of a periodical printed publication in the Committee of Information of the Ministry of Information and Social Development of the Republic of Kazakhstan **№ KZ93VPY00121157** issued **05.06.2025**
Thematic scope: *physics and chemistry.*
Periodicity: 4 times a year.
http://reports-science.kz/index.php/en/archive

© «Central Asian Academic Research Center» LLP, 2026

ACADEMIC JOURNALOF PHYSICAL AND CHEMICAL SCIENCES

2026 • 2

Бас редактор:

ЖҰРЫНОВ Мұрат Жұрынұлы, химия ғылымдарының докторы, профессор, ХҒАҚ және ҚР ҰҒА академигі, Мұнай өңдеу және мұнай-химиясы ғылыми-зерттеу институтының бас директоры (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=6602177960%; https://www.webofscience.com/wos/author/record/2017489

Редакция ұжымы:

ҚАЛИМОЛДАЕВ Мақсат Нұрәділұлы, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=56153126500, https://www.webofscience.com/wos/author/record/2428551

ӘДЕКЕНОВ Серғазы Мыңжасарұлы, химия ғылымдарының докторы, профессор, ҚР ҰҒА академигі, "Фитохимия" ғылыми-өндірістік орталығы " АҚ директоры (Қарағанды, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=7006153118, https://www.webofscience.com/wos/author/record/48648658

РАМАЗАНОВ Тілекқабыл Сәбитұлы, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі, (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=6701328029, https://www.webofscience.com/wos/author/record/13503476

ӘБИЕВ Руфат, техника ғылымдарының докторы (биохимия), профессор, Санкт-Петербург мемлекеттік технологиялық институты «Химиялық және биотехнологиялық аппаратураны оңтайландыру» кафедрасының меңгерушісі, (Санкт-Петербург, Ресей), https://www.scopus.com/authid/detail.uri?authorId=6602431781, https://www.webofscience.com/wos/author/record/1405661

ОЛИВЬЕРО Росси Сезаре, PhD (химия), Калабрия университетінің профессоры (Калабрия, Италия), https://www.scopus.com/authid/detail.uri?authorId=57221375979, https://www.webofscience.com/wos/author/record/399768

ТИГИНЯНУ Ион Михайлович, физика-математика ғылымдарының докторы, академик, Молдова Ғылым Академиясының президенті, Молдова техникалық университеті (Кишинев, Молдова), https://www.scopus.com/authid/detail.uri?authorId=7006315935, https://www.webofscience.com/wos/author/record/524462

САНГ-СУ Квак, PhD (биохимия, агрохимия), профессор, Корей Биоғылым және биотехнология ғылыми-зерттеу институты (KRIBB), өсімдіктердің инженерлік жүйелері ғылыми-зерттеу орталығының бас ғылыми қызметкері, (Дэчон, Корея), https://www.scopus.com/authid/detail.uri?authorId=59286321700, https://www.webofscience.com/wos/author/record/30028581

БЕРСІМБАЕВ Рахметқажы Ескендірұлы, биология ғылымдарының докторы, профессор, ҚР ҰҒА академигі, Л.Н. Гумилев атындағы Еуразия ұлттық университеті. (Астана, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=7004012398, https://www.webofscience.com/wos/author/record/19854255

КАЛАНДРА Пьетро, PhD (физика), наноқұрылымды материалдарды зерттеу институтының профессоры (Рим, Италия), https://www.scopus.com/authid/detail.uri?authorId=7004303066, https://www.webofscience.com/wos/author/record/616360

БОШКАЕВ Қуантай Авғазыұлы, Ph.D. Теориялық және ядролық физика кафедрасының доценті, әл-Фарабиатындағы Қазақ ұлттық университеті (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=54883880400, https://www.webofscience.com/wos/author/record/2080231

БҮРКІТБАЕВ Мұхамбетқали, химия ғылымдарының докторы, профессор, ҚР ҰҒА академигі, (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=8513885600, https://www.webofscience.com/wos/author/record/29017135

QUEVEDO Hernando, профессор, Мексика ұлттық автономиялық университеті (UNAM), Ядролық ғылымдар институты (Мехико, Мексика), https://www.scopus.com/authid/detail.uri?authorId=55989741100, https://www.webofscience.com/wos/author/record/30353742

ЖҮСІПОВ Марат Абжанұлы, физика-математика ғылымдарының докторы, теориялық және ядролық физика кафедрасының профессоры, Әл-Фараби атындағы Қазақ ұлттық университеті (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=6602166928, https://www.webofscience.com/wos/author/record/566

КОВАЛЕВ Александр Михайлович, физика-математика ғылымдарының докторы, Украина ҰҒА академигі, Қолданбалы математика және механика институты (Донецк, Украина), https://www.scopus.com/authid/detail.uri?authorId=7202799321, https://www.webofscience.com/wos/author/record/65533963

ТАКИБАЕВ Нұрғали Жабағаұлы, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі, Әл-Фараби атындағы Қазақ ұлттық университеті (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=24077239000, https://www.webofscience.com/wos/author/record/1671760

ХАРИН Станислав Николаевич, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі, (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=6701353063, https://www.webofscience.com/wos/author/record/2023295

ӘБІШЕВ Медеу Ержанұлы, физика-математика ғылымдарының докторы, профессор, ҚР ҰҒА академигі, (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=26530759900, https://www.webofscience.com/wos/author/record/1556025

ӘБІЛМАҒЖАНОВ Арлан Зайнуталлайұлы, химия ғылымдарының кандидаты, Д.В. Сокольский атындағы "Отын, катализ және электрохимия институты" АҚ Бас директорының бірінші орынбасары, (Алматы, Қазақстан), https://www.scopus.com/authid/detail.uri?authorId=57197468109, https://www.webofscience.com/wos/author/record/2024265

ACADEMIC JOURNAL OF PHYSICAL AND CHEMICAL SCIENCES
ISSN 2518-1483 (Online), ISSN 2224-5227 (Print)
Меншіктеуші: «Орталық Азия академиялық ғылыми орталығы» ЖШС (Алматы қ.).
Ақпарат агенттігінің мерзімді баспасөз басылымын, ақпарат агенттігін және желілік басылымды қайта есепке қою туралы ҚР Мәдениет және Ақпарат министрлігі «Ақпарат комитеті» Республикалық мемлекеттік мекемесі **05.06.2025 ж.** берген **№ KZ93VPY00121157** Куәлік.
Тақырыптық бағыты: *физика, химия.*
Мерзімділігі: жылына 4 рет.
http://reports-science.kz/index.php/en/archive

© «Орталық Азия академиялық ғылыми орталығы» ЖШС, 2026

ACADEMIC JOURNALOF PHYSICAL AND CHEMICAL SCIENCES

2026 • 2

Главный редактор:

ЖУРИНОВ Мурат Журинович, доктор химических наук, профессор, академик МААН и НАН РК, Генеральный директор НИИ нефтепереработки и нефтехимии (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=6602177960%; https://www.webofscience.com/wos/author/record/2017489

Редакционная коллегия:

КАЛИМОЛДАЕВ Максат Нурадилович, доктор физико-математических наук, профессор, академик НАН РК (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=56153126500, https://www.webofscience.com/wos/author/record/2428551

АДЕКЕНОВ Сергазы Мынжасарович, доктор химических наук, профессор, академик НАН РК, директор АО "Научно-производственного центра "Фитохимия" (Караганда, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=7006153118, https://www.webofscience.com/wos/author/record/48648658

РАМАЗАНОВ Тлеккабул Сабитович, (заместитель главного редактора), доктор физико-математических наук, профессор, академик НАН РК (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=6701328029, https://www.webofscience.com/wos/author/record/13503476

АБИЕВ Руфат, доктор технических наук (биохимия), профессор, заведующий кафедрой «Оптимизация химической и биотехнологической аппаратуры», Санкт-Петербургский государственный технологический институт (Санкт-Петербург, Россия), https://www.scopus.com/authid/detail.uri?authorId=6602431781, https://www.webofscience.com/wos/author/record/1405661

ОЛИВЬЕРО Росси Чезаре, доктор философии (PhD, химия), профессор Университета Калабрии (Калабрия, Италия), https://www.scopus.com/authid/detail.uri?authorId=57221375979, https://www.webofscience.com/wos/author/record/399768

ТИГИНЯНУ Ион Михайлович, доктор физико-математических наук, академик, президент Академии наук Молдовы, Технический университет Молдовы (Кишинев, Молдова), https://www.scopus.com/authid/detail.uri?authorId=7006315935, https://www.webofscience.com/wos/author/record/524462

САНГ-СУ Квак, доктор философии (PhD, биохимия, агрохимия), профессор, главный научный сотрудник, Научно-исследовательский центр инженерных систем растений, Корейский научно-исследовательский институт бионауки и биотехнологии (KRIBB), (Дэчон, Корея), https://www.scopus.com/authid/detail.uri?authorId=59286321700, https://www.webofscience.com/wos/author/record/30028581

БЕРСИМБАЕВ Рахметкажи Искендирович, доктор биологических наук, профессор, академик НАН РК, Евразийский национальный университет им. Л.Н. Гумилева (Астана, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=7004012398, https://www.webofscience.com/wos/author/record/19854255

КАЛАНДРА Пьетро, доктор философии (PhD, физика), профессор Института по изучению наноструктурированных материалов (Рим, Италия), https://www.scopus.com/authid/detail.uri?authorId=7004303066, https://www.webofscience.com/wos/author/record/616360

БОШКАЕВ Куантай Авгазыевич, PhD, преподаватель, доцент кафедры теоретической и ядерной физики, Казахский национальный университет им. Аль-Фараби (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=54883880400, https://www.webofscience.com/wos/author/record/2080231

БУРКИТБАЕВ Мухамбеткали, доктор химических наук, профессор, академик НАН РК, (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=8513885600, https://www.webofscience.com/wos/author/record/ 29017135

QUEVEDO Hernando, профессор, Национальный автономный университет Мексики (UNAM), Институт ядерных наук (Мехико, Мексика), https://www.scopus.com/authid/detail.uri?authorId=55989741100, https://www.webofscience.com/wos/author/record/30353742

ЖУСУПОВ Марат Абжанович, доктор физико-математических наук, профессор кафедры теоретической и ядерной физики, Казахский национальный университет им. аль-Фараби (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=6602166928, https://www.webofscience.com/wos/author/record/566

КОВАЛЕВ Александр Михайлович, доктор физико-математических наук, академик НАН Украины, Институт прикладной математики и механики (Донецк, Украина), https://www.scopus.com/authid/detail.uri?authorId=7202799321, https://www.webofscience.com/wos/author/record/65533963

ТАКИБАЕВ Нургали Жабагаевич, доктор физико-математических наук, профессор, академик НАН РК, Казахский национальный университет им. Аль-Фараби (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=24077239000, https://www.webofscience.com/wos/author/record/1671760

ХАРИН Станислав Николаевич, доктор физико-математических наук, профессор, академик НАН РК (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=6701353063, https://www.webofscience.com/wos/author/record/2023295

АБИШЕВ Медеу Ержанович, доктор физико-математических наук, профессор, академик НАН РК, (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=26530759900, https://www.webofscience.com/wos/author/record/1556025

АБИЛЬМАГЖАНОВ Арлан Зайнуталлаевич, кандидат химических наук, первый заместитель генерального директора АО «Институт топлива, катализа и электрохимии им. Д.В. Сокольского», (Алматы, Казахстан), https://www.scopus.com/authid/detail.uri?authorId=57197468109, https://www.webofscience.com/wos/author/record/2024265

ACADEMIC JOURNAL OF PHYSICAL AND CHEMICAL SCIENCES
ISSN 2518-1483 (Online), ISSN 2224-5227 (Print)
Собственник: ТОО «Центрально-азиатский академический научный центр» (г. Алматы).
Свидетельство **№ KZ93VPY00121157** о повторной регистрации периодического печатного издания информационного агентства, информационного агентства и сетевого издания, выданное Республиканским государственным учреждением «Комитет информации» Министерства культуры и информации Республики Казахстан **05.06.2025**
Тематическая направленность: *физика, химия.*
Периодичность: 4 раза в год.
http://reports-science.kz/index.php/en/archive

© ТОО «Центрально-азиатский академический научный центр», 2026

CONTENTS

PHYSICS

CHEMISTRY

МАЗМҰНЫ

ФИЗИКА

ХИМИЯ

СОДЕРЖАНИЕ

ФИЗИКА

ХИМИЯ

ACADEMIC JOURNAL
OF PHYSICAL AND CHEMICAL SCIENCES
ISSN 2224-5227
Volume 2.
Number 358 (2026), 367–382

https://doi.org/10.32014/2026.2518-1483.458

UDC: 547.794
IRSTI: 31.21.27

©Zhortarova A.A.[1]*, Kubicek V.[2], Salkeyeva L.K.[1], Ibrayev M.K.[1],
Seidakhmetova R.B.[3], 2026.
[1]Karaganda National Research University named after Academician Ye.A. Buketov,
Karaganda, Kazakhstan;
[2]Charles University, Prague, Czech Republic;
[3]Karaganda Medical University, Karaganda, Kazakhstan.
E-mail: aygul.zhortarova.90@mail.ru

SYNTHESIS AND INVESTIGATION OF BIOLOGICAL ACTIVITY OF1,3-BIS(4-PHENYLTHIAZOL-2-YL)-2,4-BIS(N,N-DIETHYL AMINO)-1,3-DIAZO-2,4-DIPHOSPHETIDINE

Zhortarova Aigul — PhD student, Karaganda National Research University named after Academician Ye.A. Buketov, Karaganda, Kazakhstan,
E-mail: aygul.zhortarova.90@mail.ru, https://orcid.org/0000-0001-9307-2342;
Kubicek Vojtech — Doc. RNDr., PhD, Charles University, Prague, Czech Republic,
E-mail: kubicek@natur.cuni.cz, https://orcid.org/0000-0003-0171-5713;
Salkeyeva Lyazat — Doctor of Chemical Sciences, Professor, Karaganda National Research University named after Academician Ye.A. Buketov, Karaganda, Kazakhstan,
E-mail: lsalkeeva@mail.ru, https://orcid.org/0000-0003-4207-916X;
Ibrayev Marat — Doctor of Chemical Sciences, Professor, Karaganda National Research University named after Academician Ye.A. Buketov, Karaganda, Kazakhstan,
E-mail: mkibr@mail.ru, https://orcid.org/0000-0003-0798-5562;
Seidakhmetova Roza — Candidate of Medical Sciences, Professor, Karaganda Medical University, Karaganda, Kazakhstan,
E-mail: roza77124@gmail.com, https://orcid.org/0000-0002-1990-4961.

Abstract. A new four-membered P–N–P–N heterocyclic compound, 1,3-bis(4-phenylthiazol-2-yl)-2,4-bis(N,N-diethylamino)-1,3-diazo-2,4-diphosphetidine ($C_{26}H_{32}N_6P_2S_2$, M = 554.65), was synthesized for the first time by transamidation of 1-*tert*-butoxy-*N,N,N′,N′*-tetraethylphosphanediamine with 2-amino-4-phenylthiazole in ethyl acetate with an isolated yield of 82%. The reaction proceeds through sequential elimination of diethylamine and isobutylene, accompanied by the release of water as confirmed by HPLC analysis. This pathway is mechanistically distinct from the classical Arbuzov rearrangement: instead of forming the expected phosphonate or amidophosphate products, concentration of the reaction mixture promotes intramolecular cyclisation, in which the aminothiazole N–H proton attacks the *tert*-butyl oxygen, driving formation of the strained diphosphetidine ring. The structure of Compound **5** was unambiguously established by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, IR spectroscopy, high-resolution mass spectrometry, elemental analysis, and single-crystal X-ray diffraction analysis. The ^{31}P NMR chemical shift of δ 176.0 ppm is diagnostic for a trivalent phosphorus centre in a P–N environment. Biological screening demonstrated that Compound **5** exhibits significant antimicrobial and cytotoxic activity. Against *Staphylococcus aureus* ATCC 6538, the MIC was 6.3 µg/mL, equal to that of ceftriaxone and more potent than benzylpenicillin sodium salt (MIC = 12.5 µg/mL). Moderate activity was observed against *Escherichia coli* ATCC 25922 (MIC = 25 µg/mL), while no inhibitory activity was detected against *Bacillus subtilis*, *Pseudomonas aeruginosa*, or *Candida albicans*. Cytotoxic activity against *Artemia salina* nauplii was confirmed with an LC_{50} of 82.8 µg/mL, classifying Compound **5** as cytotoxically active according to Meyer et al. (1982) and indicating its potential for further evaluation against mammalian cancer cell lines.

Keywords: aminothiazole, phosphorylation, P(III) phosphoamidates, 2-amino-4-phenylthiazole, antibacterial activity, Staphylococcus aureus, cytotoxic activity, LC_{50}, Artemia salina, antitumour activity, X-ray diffraction

For citations: *Zhortarova A.A., Kubicek V., Salkeyeva L.K., Ibrayev M.K., Seidakhmetova R.B. Synthesis and Investigation of Biological Activity of 1,3-Bis(4-Phenylthiazol-2-yl)-2,4-Bis(N,N-Diethylamino)-1,3-Diaza-2,4-Diphosphétidine. Academic Journal of Physical and Chemical Sciences. 2026. No.2. Pp. 367–382. DOI: https://doi.org/10.32014/2026.2518-1483.458*

©Жортарова А.А.[1]*, Kubicek V.[2], Салькева Л.К.[1], Ибраев М.К.[1],
Сейдахметова Р.Б.[3], 2026.
[1]Академик Е.А. Бөкетов атындағы Қарағанды ұлттық зерттеу университеті,
Қарағанды, Қазақстан;
[2]Карл университеті, Прага, Чехия Республикасы;
[3]Қарағанды медицина университеті, Қарағанды, Қазақстан.
E-mail: aygul.zhortarova.90@mail.ru

1,3-БИС(4-ФЕНИЛТИАЗОЛ-2-ИЛ)-2,4-БИС(N,N-ДИЭТИЛАМИНО)-1,3-ДИАЗО-2,4-ДИФОСФЕТИДИННІҢ СИНТЕЗІ ЖӘНЕ БИОЛОГИЯЛЫҚ БЕЛСЕНДІЛІГІН ЗЕРТТЕУ

Жортарова Айгул — PhD докторант, Академик Е.А. Бөкетов атындағы Қарағанды ұлттық зерттеу университеті, Қарағанды, Қазақстан,
E-mail: aygul.zhortarova.90@mail.ru, https://orcid.org/0000-0001-9307-2342;
Kubicek Vojtech — доцент, жаратылыстану ғылымдарының докторы, PhD, Карл университеті, Прага, Чехия Республикасы,
E-mail: kubicek@natur.cuni.cz, https://orcid.org/0000-0003-0171-5713;
Салькеева Лязат — химия ғылымдарының докторы, профессор, Академик Е.А. Бөкетов атындағы Қарағанды ұлттық зерттеу университеті, Қарағанды, Қазақстан,
E-mail: lsalkeeva@mail.ru, https://orcid.org/0000-0003-4207-916X;

Ибраев Марат — химия ғылымдарының докторы, профессор, Академик Е.А. Бөкетов атындағы Қарағанды ұлттық зерттеу университеті, Қарағанды, Қазақстан,
E-mail: mkibr@mail.ru, https://orcid.org/0000-0003-0798-5562;
Сейдахметова Роза — медицина ғылымдарының кандидаты, профессор, Қарағанды медицина университеті, Қарағанды, Қазақстан,
E-mail: roza77124@gmail.com, https://orcid.org/0000-0002-1990-4961.

Аннотация. Жаңа төрт мүшелі P–N–P–N гетероциклді қосылыс, 1,3-бис(4-фенилтиазол-2-ил)-2,4-бис(N,N-диэтиламино)-1,3-диазо-2,4-дифосфетидин ($C_{26}H_{32}N_6P_2S_2$, M = 554,65), этилацетатта 1-трет-бутокси-N,N,N',N'-тетраэтилфосфандиаминді 2-амино-4-фенилтиазолмен трансамидтеу арқылы бөлінген өнімнің шығымы 82% болып алғаш рет синтезделді. Реакция диэтиламин мен изобутиленнің дәйекті элиминациясы арқылы жүреді, бұған қоса ВЭСХ талдауымен расталған судың бөлінуі байқалады. Бұл механизм классикалық Арбузов қайта құрылуынан түбегейлі ерекшеленеді: күтілген фосфонат немесе амидофосфат өнімдерінің орнына реакциялық қоспаны қоюландыру молекулаішілік циклденуді ынталандырады, онда аминотиазолдың N–H протоны трет-бутил оттегіне шабуылдап, кернеулі дифосфетидин сақинасының түзілуін қоздырады. 3-ші қосылыстың құрылымы ^1H, ^{13}C және ^{31}P ЯМР-спектроскопия, ИҚ-спектроскопия, жоғары ажыратымдылықты масс-спектрометрия, элементтік талдау және монокристалдың рентгендік дифракциялық талдауы әдістерімен дәлелді түрде анықталды. ^{31}P ЯМР спектріндегі δ 176,0 м.қ. химиялық ығысуы P–N ортасындағы үш валентті фосфор орталығына тән. Биологиялық сынақтар қосылыс 3-тің айқын антимикробтық және цитотоксикалық белсенділік көрсететінін дәлелдеді. Staphylococcus aureus ATCC 6538-ге қарсы МИК 6,3 мкг/мл құрады, бұл цефтриаксонның белсенділігіне тең және бензилпенициллиннің натрий тұзынан (МИК = 12,5 мкг/мл) күштірек. Escherichia coli ATCC 25922-ге қарсы орташа белсенділік анықталды (МИК = 25 мкг/мл), ал Bacillus subtilis, Pseudomonas aeruginosa және Candida albicans-қа қарсы тежегіш белсенділік байқалмады. Artemia salina науплийлеріне қарсы цитотоксикалық белсенділік ЛК$_{50}$ = 82,8 мкг/мл мәнімен расталды, бұл Meyer et al. (1982) жіктемесі бойынша 3-ші қосылыстың цитотоксикалық белсенді ретінде сипаттауға мүмкіндік береді және оны сүтқоректілердің қатерлі ісік жасуша желілерінде одан әрі зерттеудің перспективалылығын көрсетеді.

Түйін сөздер: аминотиазол, фосфорлау, P(III) фосфоамидаттар, 2-амино-4-фенилтиазол, антибактериялық белсенділік, Staphylococcus aureus, цитотоксикалық белсенділік, ЛК$_{50}$, Artemia salina, ісікке қарсы белсенділік, рентгендік дифракция

©Жортарова А.А.[1]*, Kubicek V.[2], Салькева Л.К.[1], Ибраев М.К.[1],
Сейдахметова Р.Б.[3], 2026.
[1]Карагандинский национальный исследовательский университет имени академика Е.А. Букетова, Караганда, Казахстан;
[2]Карлов университет, Прага, Чешская Республика;
[3]Карагандинский медицинский университет, Караганда, Казахстан.
E-mail: aygul.zhortarova.90@mail.ru

СИНТЕЗ И ИССЛЕДОВАНИЕ БИОЛОГИЧЕСКОЙ АКТИВНОСТИ 1,3-БИС(4-ФЕНИЛТИАЗОЛ-2-ИЛ)-2,4-БИС(N,N-ДИЭТИЛАМИНО)-1,3-ДИАЗО-2,4-ДИФОСФЕТИДИНА

Жортарова Айгул — PhD докторант, Карагандинский национальный исследовательский университет имени академика Е.А. Букетова, Караганда, Казахстан,
E-mail: aygul.zhortarova.90@mail.ru, https://orcid.org/0000-0001-9307-2342;
Kubicek Vojtech — доцент, доктор естественных наук, PhD, Карлов университет, Прага, Чешская Республика,
E-mail: kubicek@natur.cuni.cz, https://orcid.org/0000-0003-0171-5713;
Салькеева Лязат — доктор химических наук, профессор, Карагандинский национальный исследовательский университет имени академика Е.А. Букетова, Караганда, Казахстан,
E-mail: lsalkeeva@mail.ru, https://orcid.org/0000-0003-4207-916X;
Ибраев Марат — доктор химических наук, профессор, Карагандинский национальный исследовательский университет имени академика Е.А. Букетова, Караганда, Казахстан,
E-mail: mkibr@mail.ru, https://orcid.org/0000-0003-0798-5562;
Сейдахметова Роза — кандидат медицинских наук, профессор, Карагандинский медицинский университет, Караганда, Казахстан,
E-mail: roza77124@gmail.com, https://orcid.org/0000-0002-1990-4961.

Аннотация. Впервые синтезировано новое четырёхчленное P–N–P–N-гетероциклическое соединение - 1,3-бис(4-фенилтиазол-2-ил)-2,4-бис(N,N-диэтиламино)-1,3-диазо-2,4-дифосфетидин ($C_{26}H_{32}N_6P_2S_2$, M = 554,65) методом трансамидирования 1-трет-бутокси-N,N,N',N'-тетраэтилфосфандиамина с 2-амино-4-фенилтиазолом в среде этилацетата. Выход целевого продукта составил 82 %. Установлено, что реакция протекает через последовательное отщепление диэтиламина и изобутилена с последующей внутримолекулярной циклизацией, приводящей к образованию напряжённого дифосфетидинового цикла. Предложенный механизм существенно отличается от классической перегруппировки Арбузова и сопровождается выделением воды, что подтверждено данными ВЭЖХ-анализа.

Структура синтезированного соединения была надёжно подтверждена комплексом современных физико-химических методов, включая ^{1}H-, ^{13}C- и ^{31}P ЯМР-спектроскопию, ИК-спектроскопию, высокоразрешающую масс-спектрометрию, элементный анализ и монокристальный рентгеноструктурный анализ. Значение химического сдвига ^{31}P ЯМР (δ = 176,0 м.д.) свидетельствует о наличии трёхвалентного атома фосфора в P–N-окружении.

Биологический скрининг показал, что полученное соединение обладает выраженной антимикробной и цитотоксической активностью. В отношении *Staphylococcus aureus* ATCC 6538 минимальная ингибирующая концентрация составила 6,3 мкг/мл, что сопоставимо с активностью цефтриаксона и превышает эффективность бензилпенициллина натриевой соли (МИК = 12,5 мкг/мл). В отношении *Escherichia coli* ATCC 25922 выявлена умеренная активность (МИК = 25 мкг/мл), тогда как против *Bacillus subtilis*, *Pseudomonas aeruginosa* и *Candida albicans* ингибирующего действия не обнаружено.

Цитотоксическая активность соединения подтверждена в тесте с науплиями *Artemia salina* (ЛК$_{50}$ = 82,8 мкг/мл). Согласно классификации Meyer et al. (1982), исследуемое соединение относится к цитотоксически активным веществам и может рассматриваться в качестве перспективного объекта для дальнейших исследований противоопухолевой активности на клеточных линиях млекопитающих.

Ключевые слова: аминотиазол, фосфорилирование, P(III) фосфоамидаты, 2-амино-4-фенилтиазол, антибактериальная активность, Staphylococcus aureus, цитотоксическая активность, ЛК$_{50}$, Artemia salina, противоопухолевая активность, рентгеноструктурный анализ

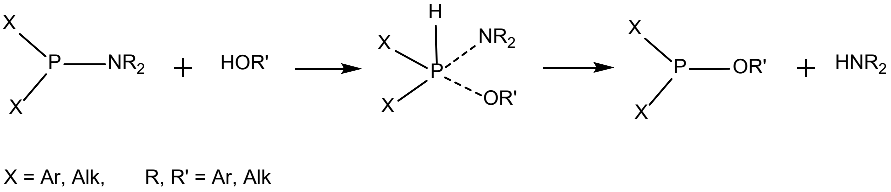
Introduction. The importance of phosphorus chemistry has not diminished and remains a focus of researchers' attention, as evidenced by the fact that the European Chemical Society (EuChemS) and the European Parliament (Science and Policy Seminar, 25 May 2023) have recognized phosphorus as one of the key chemical elements in everyday life (Jakub Adamek et al., 2023). Phosphorus is not only a component of the human body but also the foundation of the agrochemical industry. It is often mentioned today that we are living in the 'golden age of phosphorus chemistry'. In this context, organophosphorus chemistry is also becoming increasingly important as one of the fastest-growing sectors of organic chemistry. Phosphorus-containing compounds (also known as P-compounds) are widely used as reagents (starting materials, precursors of active intermediates such as ylides or iminium-type cations, etc.), catalysts (PTC, organocatalysis) and solvents (PIL) (He et al., 2009; Bradaric et al., 2003; Allen et al., 2023; Maryanoff et al., 1989).

Thanks to the interesting properties of P-compounds (particularly their biological activity), they are widely used in medicine (for example, in treatments for bone diseases, anti-cancer and antiviral agents, as well as anti-helminthic drugs; and in veterinary medicine), agriculture (for example, pesticides) and industry (e.g. the production of lubricants or plastics). However, in an era of much-needed environmental care, we face new challenges. Innovative approaches to the synthesis and isolation of P-compounds (considering aspects of green chemistry and sustainable development), as well as their responsible use and disposal (neutralization), may prove decisive in the near future (Kolodiazhnyi et al., 2020; Russell et al., 2020; Caminade et al., 2020).

As part of our ongoing research of heterocyclic phosphorus compounds, we have investigated phosphorylation reactions involving thiazoles of various structures. The literature describes a wide variety of methods for introducing P(III) and P(V) atoms into heterocyclic systems, which have found widespread practical application as effective medicinal compounds. This is, on the one hand, due to the broad potential for biological activity of the basic pharmacophore, which is a five-membered heterocycle, namely: thiazole, oxazole, thiadiazole, etc. Thus, classical concepts regarding the phosphorylation reaction of P(III) acids with amides are extensively described in the review by E.E. Nafantiev and M.K. Grachev (Nafantiev et al., 1994). This review covers a wide range of studies in which P(III) acid amides act as phosphorylating agents and various amines and alcohols serve as substrates. It is noted that P(III) acid amides have found widespread application in the phosphorylation of alcohols, phenols and amines, with the authors emphasizing the untapped potential of P(III) acid amides in their ability to phosphorylate a wide range of proton-donating nucleophiles, which demonstrates the value of these compounds in synthetic chemistry.

It is well known that there are thousands of studies describing the phosphorylation of various compounds using phosphamidates. Nevertheless, many theoretical questions concerning the reactivity of phosphamidates and the mechanisms of the reactions involved remain unresolved, although there are numerous hypotheses on this subject in the literature.

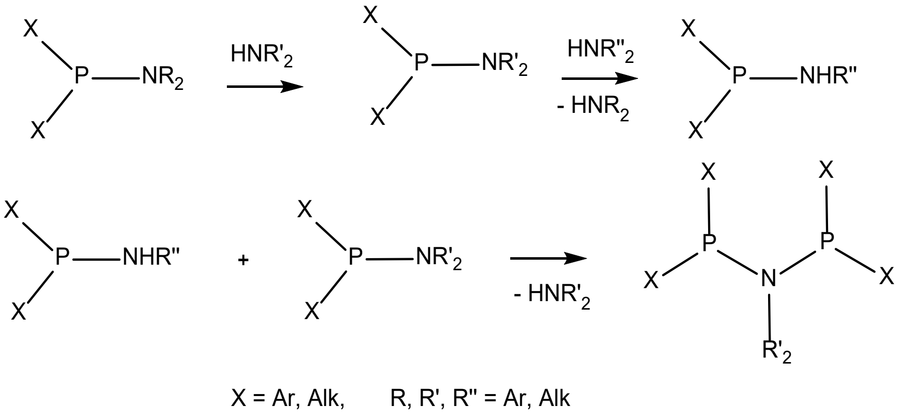
Phosphorylation reactions involving phosphamides of alcohols and phenols have been the most extensively studied *(Scheme 1).* Some authors propose an ‘addition-elimination’ mechanism involving the formation of a dihydrophosphorane intermediate, which decomposes to release an amine (Burgada et al., 1974; Pudovik et al., 1975; Terentyeva et al., 1976;).



Scheme 1. Phosphorylation reactions involving phosphamides of alcohols and phenols.

Regarding the mechanism of this reaction, there were suggestions, on the one hand, of *P*-protonation by phosphamidate with the formation of a quasi-phosphonium intermediate and the subsequent formation of an ester; and, on the other hand, of *N*-protonation, as well as the suggestion that a four-membered transition state is formed. Moreover, some authors argued that *N*-protonation is the energetically more favourable process based on quantum-chemical calculations. Other authors leaned towards the initial P-protonation process or the possibility of parallel N- and P-protonation processes (Pudovik et al., 1977). Alcoholysis, phenolysis and aminolysis by phosphoric acid (III) amides are related reactions; however, an analysis of these transformations reveals their differences, since aminolysis, unlike phenolysis and alcoholysis, may involve double or triple phosphorylation in the case of primary and secondary amines.

Many authors argue that the mechanism of transamidation involves the formation of a phosphorane and its subsequent decomposition *(Scheme 2).* (Nielsen and Dahl et al., 1984; Dahl et al., 1981; Houalla et al., 1977; Jeanncaux et al., 1984).



Scheme 2. Transamidation mechanism involving phosphorane formation.

A suitable synthetic method for the preparation of complex phosphamides is the aminolysis of the simplest members of this class of compounds. In particular, phosphorous acid hexamethyl(ethyl)triamides, being readily available commercial products, can serve as key substances in the preparation of more complex triamides (Maier et al., 1964; Houalla et al., 1965; Hussain et al., 1988).

It has been shown that the aromatic amine o,o'-diaminodiphenyl forms 4,5,6,7-diphenyl-1,2,3-diphosphorinan when it reacts with di- and triamides of phosphorous acid (Nifantiev et al., 1994).

Materials and methods. All chemicals were of analytical grade and procured from Sigma-Aldrich suppliers without the need for further purification. Reactions underwent monitoring via thin layer chromatography (TLC) on F254 silica gel coated plates from Merck. Bruker 400 and 600 MHz NMR spectrometer was used to record the ^{1}H and ^{13}C NMR spectra in CDCl$_3$ along with TMS functioning as the internal standard. Mass spectra were taken using a Shimadzu mass spectrometer. IR spectra were taken with a Thermo Scientific Nicolet 6700 FTIR spectrometer (Madison, WI, USA). The melting point was determined using a Buchi Melting point M-560 instrument. Diffraction experiment was performed on a Bruker D8 VENTURE Kappa Duo PHOTON100 by IμS micro-focus sealed tube either with MoKα (λ= 0.71073) radiation at a temperature of 120(2) K for 5, or CuKα (λ = 1.54178) for 1 at a temperature of 150(2) K.

Synthesis Section. 1-tert-butoxy-N,N,N',N'-tetraethylphosphanediamine.(1) 105.30 g (0.5 mol) of tetraethylenediamine dichlorophosphite was placed in a four-necked flask fitted with a mechanical stirrer, a thermometer, a reflux condenser and a dropping funnel, in 2 L of benzene. Under vigorous stirring at 0–5 °C, a mixture of 37.00 g (0.5 mol) of *tert*-butyl alcohol and 55.6 g (0.55 mol) of triethylamine in 200 ml of benzene was added. After stirring at room temperature for 2–3 hours, the triethylamine hydrochloride precipitate was filtered off, the solvent was removed under vacuum using a water jet pump (30–40 mm Hg), and distillation of the residue yielded 102.9 g (83% of the theoretical yield) 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetraethylphosphanediamine with a boiling point of 52–53 °C (0.07 mm Hg), d_4^{20} 0.8996, n_D^{20} 1.4510. Found, %: C 58.30;

H 11.45; N 11.38; P 12.25. $C_{12}H_{29}N_2OP$. Calculated, %: C 58.06; H 11.69; N 11.29; P 12.59. ^{31}P 124 m.d., ^{1}H 1.17 m.d. (CH_3, 12H, t, 3JHH 7 Hz), 1.43 m.d. [$(CH_3)_3C$, 9H, c], 3.07 m.d. (CH_2, 12H, m).

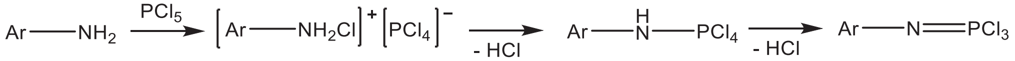
1,3-Bis(4-phenylthiazol-2-yl)-2,4-bis(N,N-diethyl amino)-1,3-diazo-2,4-diphosphetidine. (5). To 2.48 g (0.01 mol) of 1-*tert*-butoxy-*N*,*N*,*N'*,*N'*-tetraethylphosphanediamine, 1.76 g (0.01 mol) of 2-amino-4-phenylthiazole was added in 100 mL of ethyl acetate. The reaction mixture was heated with stirring until the evolving diethylamine, the amount of which corresponds to the stoichiometry of the reaction (1.10 g), had completely evaporated (93%). The resulting yellow, oily substance crystallized upon prolonged standing. The product yield was 2.17 g (82%), mp 162°C. ^{1}H NMR (300 MHz, chloroform-d) δ 7.88 (d, J = 7.2 Hz, 4H, H-2,6 Ph), 7.44 (t, J = 7.5 Hz, 4H, H-3,5 Ph), 7.35 (t, J = 7.3 Hz, 2H, H-4 Ph), 6.92 (s, 2H, H-5 Thz), 3.14 (m, 8H, NCH_2), 1.07 (t, J = 7.1 Hz, 12H, NCH_2CH_3). ^{13}C NMR (75 MHz, chloroform-d) δ 162.8 (d, J = 8.1 Hz, C2-Thz), 162.6 (d, J = 7.4 Hz, C2-Thz), 149.5 (C4-Thz), 129.6 (C-para Ph), 128.4 (C-ortho Ph), 128.1 (C-meta Ph), 126.2 (C-ipso Ph), 110.1 (C5-Thz), 42.6 (NCH_2), 42.4 (NCH_2), 15.2 (NCH_2CH_3). ^{31}P NMR (121 MHz, chloroform-d) δ 176.0 Chemical Formula: $C_{26}H_{32}N_6P_2S_2$. Exact Mass: 554.16. Molecular Weight: 554.65. m/z: 554.16 (100.0%), 555.16 (31.9%), 556.16 (10.2%), 556.17 (3.9%), 557.16 (2.7%). Elemental Analysis: C, 56.30; H, 5.82; N, 15.15; P, 11.17; S, 11.56.

Antimicrobial Assay (Serial Broth Dilution / MIC). Test microorganisms (ATCC strains) were cultured on freshly streaked agar plates at 37 °C for 24 h (bacteria) or at 30 °C for 48 h (Candida albicans). Inocula were prepared in nutrient broth at a concentration of 1×10^6 CFU/mL. Compound 5 was dissolved in ethanol and serially diluted in nutrient broth to yield final concentrations of 1.56, 3.13, 6.25, 12.5, 25, and 50 μg/mL. A 0.1 mL aliquot of the microbial suspension was added to each tube. Tubes inoculated without the test compound served as negative controls. After incubation at 37 °C for 24 h (bacteria) or 48 h (*c. albicans*), turbidity was assessed visually. The minimum inhibitory concentration (MIC) was defined as the lowest concentration at which no visible growth was observed. All results were averaged over three independent experiments.

Cytotoxicity Assay (Artemia salina Brine Shrimp Lethality). Artemia salina eggs were hatched in artificial seawater at 25–28 °C for 48 h to obtain nauplii. Compound 5 was dissolved in ethanol at 1 mg/mL, and aliquots of 500, 50, and 5 μL were dispensed into separate vials in triplicate. After evaporation of ethanol, 5 mL of artificial seawater was added to each vial, yielding final concentrations of 100, 10, and 1 μg/mL. Ten nauplii were added to each vial, and the vials were incubated at room temperature under illumination for 24 h. Mortality was assessed by counting live and dead larvae. LC_{50} values and 95% confidence intervals were calculated using probit analysis (Meyer et al., 1982).

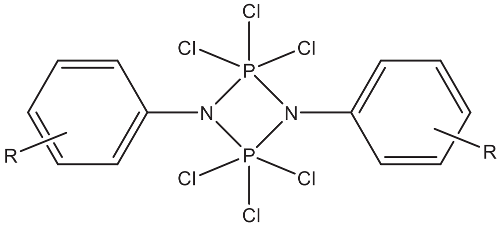
Results and Discussion. The question of the phosphorylation of various classes of compounds, including heterocyclic systems such as thiazoles, oxazoles, thiadiazoles, etc., remains at the forefront of researchers' attention, as it is: They open the way to the synthesis of a wide variety of derivatives with predictable chemical and practical properties, including those with the potential to be new pharmaceutical substances. The potential for the application of organic phosphorus compounds in a wide range of areas is significant and, in most cases, has not been thoroughly investigated. Currently, a wide range of organic compound classes are being investigated for the introduction of variously coordinated phosphorus atoms, which exhibit and are being investigated for a wide range of practically useful properties.

Existing problems and prospects for the development of organic phosphorus chemistry in the field of strategy synthesis and the study of the properties of five-membered nitrogen-containing heterocycles as valuable tools in modern synthetic chemistry are widely discussed in the literature. It is important to note an earlier publication, namely the doctoral dissertation of the German chemist Wachtler Düter (Wachtler Düter et al., 1976), which considers the formation of four-membered cycles consisting of two phosphorus atoms and two nitrogen atoms. Such systems were formed on the basis of the interaction of substituted anilines and PCl_5 *(Scheme 3).*



Scheme 3. Four-membered phosphorus–nitrogen heterocycle (P_2N_2 ring).

The author (Wachtler et al., 1976) demonstrates the possibility of the final isomer of trichlorophosphane undergoing dimerisation to form corresponding four-membered rings containing two phosphorus and two nitrogen atoms. The structure of the compound *(Scheme 4)* obtained by (Wachtler et al., 1976) is proven by ^{31}P NMR data, where the phosphorus atom resonates in the (+70) – (+85) ppm region.



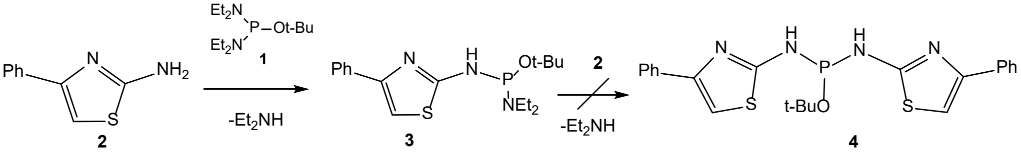
Scheme 4. Four-membered P_2N_2 heterocycle (diazadiphosphetidine ring system).

In continuation of the research into the phosphorylation of five-membered heterocyclic systems, derivatives of amino thiazoles are undoubtedly of interest. Considering that, to date, there is practically no information in this area, except for the brief report previously published by us (Sal'keeva et al., 2014).

Phosphorylated thiazoles are of significant theoretical and practical interest, yet remain a relatively unexplored area of research. At various times, attempts have been made to synthesize phosphorus-containing derivatives of thiazole and its homologues. In particular, the introduction of 2-aminothiazole into direct condensation with aromatic aldehydes and dialkyl phosphites in the presence of alkylates of alkaline metals failed, which is evidently due to the low basicity of 2-aminothiazole (pK_a – 5.39). However, phosphonometallation of 2-aminothiazole was achieved by reacting dialkylphosphites with diacetylbenzaldehyde in the presence of boron trifluoride etherate. Equilibrium between amino- and imino-structures was established, and a significant shift in equilibrium towards the amino-form was demonstrated.

As the analysis of the literature shows, there is practically no information on the interaction of trivalent phosphorus compounds with 2-amino-4-phenylthiazole 2 or its derivatives. The fundamental difference in the reactivity of phosphorus(III) compounds undoubtedly makes the outcome of the interaction unclear. However, 2-amino-4-phenylthiazole derivatives containing a phosphorus atom can be modified to produce pentavalent phosphorus derivatives, making them unique synthons for further chemical transformations.

It is known that amidophosphonates are of particular interest among phosphorus compounds. They can easily exchange the amido group under the influence of alcohols, amines and phenols. This method is very convenient for obtaining phosphoramidites that are difficult to obtain through direct synthesis. To this end, we investigated the transamidation reaction of tetraethyl diammido-*tert*-butylphosphite 1 (δ ^{31}P 124 ppm) with 2-amino-4-phenylthiazole *2 (Scheme 5),* resulting in the formation of diethylamido-(4-phenylthiozole-2-amido)-*tert*-butylphosphite 3. In the transamidation of tetraethylamido-*tert*-butylphosphite in the same conditions with two moles of 2-amino-4-phenylthiazole 2, only one mole of diethylamine was produced. When an additional mole of phosphite was added to the reaction mixture, an amido-phosphite 3 was isolated and identified. Thus, it is not possible to introduce two 2-amino-4-phenylthiazole groups to the P(III) atom, apparently due to steric hindrance and 4 was not isolated.



Scheme 5. Sequential phosphorylation and coupling of 2-aminothiazole affording a bis(phosphoramide) product.

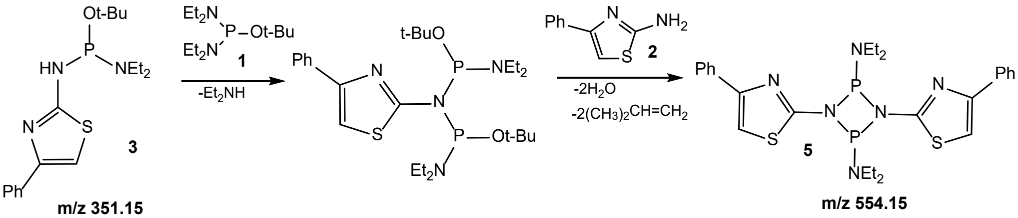
The IR spectrum of compound 3 shows absorption bands at 1441 and 1598 cm^{-1}, which are attributed to C=C vibrations. There is an absorption band at 1483 cm^{-1}, which corresponds to C=N vibrations, and N-H vibrations resonate in the characteristic region of 3435 cm^{-1}. Absorption bands of the C-O-C bond are observed at 1071 cm^{-1}.

In the ^{1}H NMR spectrum of compound 3, measured in DMSO-d$_6$, the phenyl ring protons appear as a multiplet in the region 7.22–7.40 ppm, and the singlet of the *tert*-butyl group is observed at 1.40 ppm. A triplet of methyl protons with a spin-spin coupling constant of $^3J_{HH}$ = 7 Hz is located at 1.16 ppm. A multiplet of methylene protons is observed at 2.59 ppm. The signal of the N-H group proton appears as a singlet at 7.80 ppm, and the signal of the proton of the C5 thiazole ring appears as a singlet at the characteristic 7.05 ppm. IR and NMR spectra of compound 3. Systematic investigation of the reactivity and structural features of phosphorilated heterocyclic amines showed that the structures of phosphorilated and thiophosphorilated 2-aminothiazoles and 2-aminothiazolines are predominantly in the imino form. However, in the case of phosphonalkylated derivatives of thiazole, a significant shift in the amine-imine tautomer equilibrium towards the amine form has been observed.

Analysis of data from infrared and nuclear magnetic resonance spectroscopy allows the structure of diethylamido-(4-phenylthiazol-2-yl)-*N*,*N*'-bis(*tert*-butylphosphin) phosphoramidite 3 to be assigned an amino form. This is based on the signal of the proton of the thiazole ring at C5, which was found in the characteristic region of 7.05 m.d., as well as the vibrational modes of the endocyclic C=N bond at 1483 cm^{-1}, which differ significantly from the vibrational modes of the exocyclic C=N bond, resonating 20-40 cm^{-1} higher. Furthermore, the existence of amine or imine forms of heterocyclic compounds depends significantly on the basicity of the exocyclic nitrogen atom. The presence of a phenyl group in the 4-position of 2-aminotriazole significantly reduces the basicity of the amino group and shifts the tautomer equilibrium towards the amine form.

To vary the conditions for the transamidation reaction of tetraethyl diammido-*tert*-butylphosphite 1 with 2-amino-4-phenylthiazole 2, we attempted to use benzene as a solvent. When choosing a solvent, we prioritised the inertness of the reagents to the chosen solvent. However, it turned out that the process in benzene is ambiguous and leads to the formation of a mixture of reaction products 3.

It is clear that the by-product of the transamidation reaction, diethylamine, is capable of interacting with the starting material, tetraethyldiamide-*tert*-butylphosphite 1, to form hexaethyltriamidophosphite and *tert*-butanol. The resulting tertiary butanol then reacts with 2, forming the compound 3. This direction of the reaction can be explained by the poorer solubility of 2-amino-4-phenylthiazole 2 in the less polar solvent, benzene, than in the more polar solvent, ethyl acetate, which reduces the likelihood of collisions between molecules of tetraethylamido-tert-butylphosphite 1 and 2-amino-4-phenylthiazole 2 and increases the likelihood of side reactions of transamidation and alcoholysis *(Scheme 6)*.



Scheme 6. Construction of bis(thiazolyl) phosphoramide compounds via phosphoryl coupling reactions.

The reactions were controlled using mass spectrometry. According to the results of the mass spectra analysis, a product 3 with m/z 351 is formed in the first stage of the reaction, which corresponds to the structure 3. The product 5 1,3-bis(4-phenylthiazol-2-yl)-2,4-bis(*N*,*N*-diethylamino)-1,3-diazodiphosphorine (III), with m/z 554 identified by us, the structure of which has been proven by X-ray diffraction analysis (Figure 1).

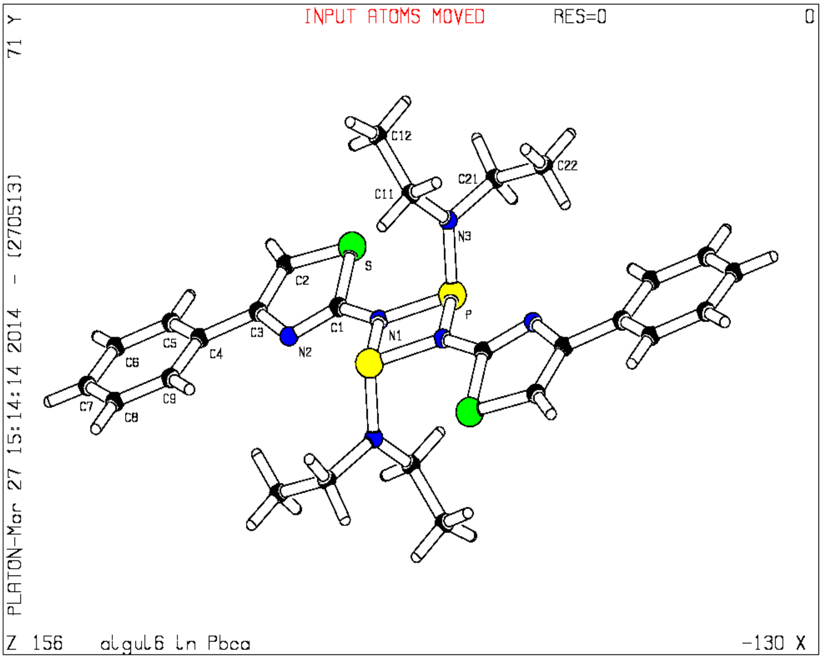


Figure 1. X-ray diffraction analysis of 1,3-bis(4-phenylthiazol-2-yl)-2,4-bis(N,N-diethylamino)-1,3-diazo-2,4-diphosphetidine.

The final product 5 of the reaction was diphosphetidine structure with a four-membered ring containing two phosphorus (III) atoms and two nitrogen atoms (Figure 1). It should be noted that the reaction products were identified as the gas isobutylene, which was detected by the water displacement method.

A notable aspect of the reaction is the release of isobutylene, which typically leads to the formation of a stable phosphoramidate group. This reaction course is characteristic of full phosphoric acid esters and phosphoric acid amides. However, in the presence of a tertiary butoxy group, it is known that the second stage of the Arbusov reaction scheme proceeds much faster and leads to the formation of corresponding phosphonates or amido phosphates.

However, in our case, we observed the release of isobutylene, but did not observe the formation of phosphonate and amido-phosphate compounds. This behaviour is clearly related to the fact that, under the reaction conditions with constant removal of the released diethylamine, the reaction mixture is concentrated, which brings the reaction centres closer together. Consequently, the proton of the amino group attacks the oxygen atom of the tertiary butyl group, which explains the formation and release of a water molecule.

Antimicrobial Activity. Experimental Overview. The in vitro antimicrobial activity of 5 was evaluated against five reference microorganisms: two Gram-positive bacteria (Staphylococcus aureus ATCC 6538 and Bacillus subtilis ATCC 6633), two Gram-negative bacteria (Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC

27853), and the yeast Candida albicans ATCC 10231. All strains were obtained from the American Type Culture Collection (ATCC). The minimum inhibitory concentration (MIC) was determined by the serial broth dilution method at concentrations ranging from 1.56 to 50 µg/mL. All assays were performed in triplicate, and results are presented as mean values. Ceftriaxone, benzylpenicillin, and nystatin served as positive controls.

MIC Data — Compound 5 vs. Reference Drugs. Table 1. Presents the MIC values (µg/mL) for compound 5 and the reference drugs against each microorganism. "—" indicates no detectable inhibitory activity within the tested concentration range.

Table 1. Antimicrobial activity (MIC values, µg/mL) of **5** and reference drugs.

Compound / Agent	*S. aureus* ATCC 6538	*B. subtilis* ATCC 6633	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*C. albicans* ATCC 10231
Compound **5**	6.3	—	25	—	—
Reference drugs (positive controls)					
Ceftriaxone	6.3	12.5	6.3	6.3	—
Benzylpenicillin sodium salt	12.5	25	25	50	—
Nystatin	—	—	—	—	12.5

Activity Against Gram-Positive Bacteria. Compound 5 showed pronounced antibacterial activity against *S. aureus* ATCC 6538, with an MIC of 6.3 µg/mL, equal to that of ceftriaxone (MIC = 6.3 µg/mL) and twofold lower than benzylpenicillin (MIC = 12.5 µg/mL), indicating higher potency against this strain. No inhibitory activity was detected against *B. subtilis* ATCC 6633.

Activity Against Gram-Negative Bacteria. Against *E. coli* ATCC 25922, Compound 5 showed moderate activity (MIC = 25 µg/mL), four times higher than ceftriaxone (MIC = 6.3 µg/mL) and equivalent to benzylpenicillin (MIC = 25 µg/mL). No activity was detected against *P. aeruginosa* ATCC 27853, consistent with its known resistance profile.

Antifungal Activity. Compound 5 showed no detectable activity against *C. albicans* ATCC 10231 at the tested concentrations (1.56–50 µg/mL), whereas the reference drug nystatin exhibited an MIC of 12.5 µg/mL. These results indicate that Compound 5 lacks significant antifungal activity under the applied conditions.

Structure–Activity Relationship. From a structure–activity relationship perspective, the pronounced anti-staphylococcal activity of Compound 5 (MIC = 6.3 µg/mL against S. aureus ATCC 6538) can be attributed to the synergistic effect of the 4-phenylthiazolyl pharmacophore and the P(III)-containing diphosphetidine ring. The four-membered P–N–P–N cycle, with its highly polar phosphorus–nitrogen bonds and electron-rich phosphorus centres, likely enhances interaction with bacterial membrane components or intracellular targets. The moderate activity against E. coli (MIC = 25 µg/mL) and the absence of activity against P. aeruginosa and C. albicans suggest that the antibacterial spectrum is primarily directed at Gram-positive organisms, which is consistent with the lipophilicity profile of the compound and the known selectivity of structurally related phosphorylated heterocycles.

Cytotoxic Activity. Experimental Overview. The cytotoxic activity of Compound 5 was evaluated using the *Artemia salina* (Leach) brine shrimp lethality assay, following the method of Meyer et al. (1982). The assay was performed on 2-day-old nauplii under in vitro conditions. LC_{50} values with 95% confidence intervals were calculated by probit analysis based on 24 h mortality counts. Dactinomycin (actinomycin D; Sigma-Aldrich) served as the positive control, and DMSO in equivalent volumes was used as the solvent control.

LC_{50} Data — Compound 5 vs. Reference Drug

Table 2. Cytotoxic activity (LC_{50} values, µg/mL) of Compound **5** and reference drug against Artemia salina larvae.

Compound / Agent	LC_{50} (µg/mL)
Compound **5**	82.8
Dactinomycin (positive control)	46.2

Interpretation. Compound **5** exhibited cytotoxic activity against *Artemia salina* nauplii, with an LC_{50} of 82.8 µg/mL. According to Meyer et al. (1982), substances with LC_{50} < 1000 µg/mL are classified as cytotoxic, and therefore Compound **5** is considered cytotoxically active. Its LC_{50} is approximately 1.8-fold higher than that of dactinomycin (LC_{50} = 46.2 µg/mL), indicating a lower but noteworthy level of activity. The brine shrimp lethality assay is widely recognized as a preliminary in vivo screening model for cytotoxicity. A correlation between *Artemia salina* lethality and cytotoxicity against human cancer cell lines has been reported. Based on these results, Compound **5** may be considered a candidate for further evaluation against human cancer cell lines, including the NCI-60 panel, to assess its antitumor potential.

Conclusion. A novel four-membered P–N–P–N heterocyclic compound, 1,3-bis(4-phenylthiazol-2-yl)-2,4-bis(*N*,*N*-diethylamino)-1,3-diazo-2,4-diphosphetidine **5** ($C_{26}H_{32}N_6P_2S_2$, M = 554.65), has been synthesized for the first time by transamidation of 1-*tert*-butoxy-*N*,*N*,*N*',*N*'-tetraethylphosphanediamine with 2-amino-4-phenylthiazole in ethyl acetate with an isolated yield of 82%. The reaction proceeds through sequential elimination of diethylamine and isobutylene, accompanied by the release of water as confirmed by HPLC analysis of the reaction mixture. This pathway is mechanistically distinct from the classical Arbuzov rearrangement: instead of forming the expected phosphonate or amidophosphate products, concentration of the reaction mixture promotes intramolecular cyclisation, in which the aminothiazole N–H proton attacks the *tert*-butyl oxygen, driving formation of the strained diphosphetidine ring.

The structure of Compound 5 was unambiguously established by a combination of ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, IR spectroscopy, high-resolution mass spectrometry, elemental analysis, and single-crystal X-ray diffraction analysis. The ^{31}P NMR chemical shift of δ 176.0 ppm is diagnostic for a trivalent phosphorus centre in a P–N environment, and the X-ray data confirmed eight crystallographically independent molecules in the unit cell, representing both CIS and TRANS configurational isomers.

Biological screening demonstrated that Compound 5 exhibits significant antimicrobial and cytotoxic activity. Against *Staphylococcus aureus* ATCC 6538, the compound showed an MIC of 6.3 μg/mL, equal to that of ceftriaxone and more potent than benzylpenicillin sodium salt (MIC = 12.5 μg/mL). Moderate activity was observed against *Escherichia coli* ATCC 25922 (MIC = 25 μg/mL), while no inhibitory activity was detected against *Bacillus subtilis*, *Pseudomonas aeruginosa*, or *Candida albicans* at the tested concentrations. The antibacterial selectivity toward Gram-positive organisms may reflect the compound's lipophilicity and the known pharmacology of phosphorylated heterocyclic aminothiazoles. Cytotoxic activity against *Artemia salina* nauplii was confirmed, with an LC_{50} of 82.8 μg/mL, classifying Compound 5 as cytotoxically active according to Meyer et al. (1982) and indicating its potential for further evaluation against mammalian cancer cell lines.

The results of this study expand the scarce literature on the phosphorylation of aminothiazoles by P(III) ester amides and demonstrate that the four-membered 1,3,2,4-diphosphetidine ring system is accessible from commercially available precursors under mild conditions. The synthetic approach described here, combined with the promising biological profile of Compound 3, provides a rational basis for the design of novel phosphorus-containing heterocyclic compounds as potential anti-infective and antitumour agents. Further work will focus on structure optimisation, expansion of the biological target panel including NCI-60 cancer cell line screening, and mechanistic investigation of the antibacterial mode of action.

References

Adamek J. (2023) Special Issue "Organophosphorus Chemistry: A New Perspective". Molecules. – No. 28. – P. 4752. https://doi.org/10.3390/molecules28124752 (in English).

Allen D.W., Loakes D., Tebby J. (2016) Organophosphorus Chemistry. The Royal Society of Chemistry: London, UK. – Vol. 45. (in English).

Bradaric C.J., Downard A., Kennedy C., Robertson A.J., Zhou Y. (2003) Industrial preparation of phosphonium ionic liquids. Green Chem. – No. 5. – P. 143-152. https://doi.org/10.1039/b209734f (in English).

Burgada R., Laurenço C. (1974) Journal of Organometallic Chemistry. – No. 66(2). – P. 255-270. (in English).

Caminade A.-M. (2020) Phosphorus Dendrimers as Nanotools against Cancers. Molecules. – No. 25. – P. 3333. https://doi.org/10.3390/molecules25153333 (in English).

Dahl O. (1981) Phosphite coupling agents in oligonucleotide synthesis. Tetrahedron Letters. – No. 22(34). – P. 3281-3284. (in English).

He R., Ding C., Marouka K. (2009) Phosphonium Salts as Chiral Phase-Transfer Catalysts: Asymmetric Michael and Mannich Reactions of 3-Aryloxindoles. Angew. Chem. – No. 48. – P. 4559-4561. https://doi.org/10.1002/anie.200901277 (in English)

Houalla D., Osman F.H., Sanchez M., Wolf R. (1977) Nouveau mode de formation de la liaison phosphore-hydrogène: ouverture d'un cycle oxazaphospholane par les alcools et les amines. Tetrahedron Letters. – No. 18(35). – P. 3041-3044. (in French)

Houalla D., Sanchez M., Wolf R. (1965) Sur la structure des composés issus de la réaction entre les α-aminoalcools et les triaminophosphines. Bulletin de la Société Chimique de France. – No. 8. – P. 2368-2373. (in French).

Hussain L.A., Elias A.J., Rao M.N.S. (1988) Reaction of 2-chloro-1,3,2-oxazaphospholanes with silylated nitrogen and sulfur nucleophiles. Tetrahedron Letters. – No. 29(46). – P. 5983-5986. (in English).

Jeanneaux F., Riess J.G., Wachter J. (1984) Structural and coordination chemistry of 2-amino-1,3,2-

oxazaphospholanes and their pentacoordinated oligomers. Inorg. Chem. – No. 23. – P. 3036-3043. (in English).

Kolodiazhnyi O.I. (2021) Phosphorus Compounds of Natural Origin: Prebiotic, Stereochemistry, Application. Symmetry. – No. 13. – P. 889. https://doi.org/10.3390/sym13050889 (in English).

Maier L. (1964) Organic Phosphorus Compounds. VII. A Convenient Synthesis of Tertiary Phosphine Sulfides and Phosphonothioic Dichlorides. Helvetica Chimica Acta. – No. 47(7). – P. 2129-2136. (in English).

Maryanoff B.E., Reitz A.B. (1989) The Wittig olefination reaction and modifications involving phosphoryl-stabilized carbanions. Stereochemistry, mechanism, and selected synthetic aspects. Chem. Rev. – No. 89. – P. 863-927. https://doi.org/10.1021/cr00094a007 (in English).

Nafant'ev E.E., Grachev M.K. (1994) Amidy trekh"valentnogo fosfora kak fosforyliruyushchiye agenty dlya spirtov i aminov [Amides of trivalent phosphorus acids as phosphorylating agents for alcohols and amines]. Russian Chemical Reviews. – No. 63(7). – P. 602-637. https://doi.org/10.1070/RC1994v063n07ABEH000106 (in Russian).

Nielsen J., Dahl O. (1984) Mechanism of the phosphoramidite phosphite-coupling reaction in oligonucleotide synthesis. Journal of the Chemical Society, Perkin Transactions 2. – No. 3. – P. 553-558. (in English).

Pudovik A.N., Batyeva E.S., Ofitserov E.N. (1977) O mekhanizme reaktsii amidofosfitov s elektrofilnymi reagentami [On the mechanism of the reaction of amidophosphites with electrophilic reagents]. Doklady Academy of Sciences of the USSR. – Vol. 232. – P. 1092-1095. (in Russian).

Pudovik M.A., Terent'eva S.A., Samitov Yu.Yu., Pudovik A.N. (1975) Reactions of 2-Amino-1,3,2-oxazaphospholanes with Acyl Halides. Journal of General Chemistry. – No. 45. – P. 226. (in English).

Russell R.G.G. (2011) Bisphosphonates: The first 40 years. Bone. – No. 49. – P. 2. https://doi.org/10.1016/j.bone.2011.04.022 (in English).

Sal'keeva L.K., Voitichek P., Taishibekova E.K., Zhortarova A.A., Shibaeva A.K., Sugralina L.M., Muratbekova A.A., Sal'keev A.K. (2014) Unusual Phosphorylation of 2-Amino-4-phenylthiazole with Phosphorous Acid Ester Amides. Russian Journal of General Chemistry. – No. 84(12). – P. 2477-2479. https://doi.org/10.1134/S1070363214120275 (in English).

Terent'eva S.A., Pudovik M.A., Pudovik A.N. (1976) Interaction of 2-amino-1,3,2-oxazaphospholanes with electrophilic reagents. Bulletin of the Academy of Sciences of the USSR, Chemical Series. – P. 1897-1899. (in Russian).

Wachter J. (1976) Ein Beitrag zur Phosphor-Stickstoff Chemie. Doctoral dissertation, University of Stuttgart. – P. 1-121. (in German).

Publication Ethics and Publication Malpractice in the journals of the «Central Asian Academic Research Center» LLP (Almaty)

For information on Ethics in publishing and Ethical guidelines for journal publication see http://www.elsevier.com/publishingethics and http://www.elsevier.com/journal-authors/ethics.

Submission of an article to the National Academy of Sciences of the Republic of Kazakhstan implies that the work described has not been published previously (except in the form of an abstract or as part of a published lecture or academic thesis or as an electronic preprint, see http://www.elsevier.com/postingpolicy), that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder. In particular, translations into English of papers already published in another language are not accepted.

No other forms of scientific misconduct are allowed, such as plagiarism, falsification, fraudulent data, incorrect interpretation of other works, incorrect citations, etc. The National Academy of Sciences of the Republic of Kazakhstan follows the Code of Conduct of the Committee on Publication Ethics (COPE), and follows the COPE Flowcharts for Resolving Cases of Suspected Misconduct (http://publicationethics.org/files/u2/New_Code.pdf). To verify originality, your article may be checked by the originality detection service Cross Check http://www.elsevier.com/editors/plagdetect.

The authors are obliged to participate in peer review process and be ready to provide corrections, clarifications, retractions and apologies when needed. All authors of a paper should have significantly contributed to the research.

The reviewers should provide objective judgments and should point out relevant published works which are not yet cited. Reviewed articles should be treated confidentially. The reviewers will be chosen in such a way that there is no conflict of interests with respect to the research, the authors and/or the research funders.

The editors have complete responsibility and authority to reject or accept a paper, and they will onh accept a paper when reasonably certain. They will preserve anonymity of reviewers and promote publication of corrections, clarifications, retractions and apologies when needed. The acceptance of a paper automatically implies the copyright transfer to the National Academy of sciences of the Republic of Kazakhstan.

The Editorial Board of the National Academy of sciences of the Republic of Kazakhstan will monitor and safeguard publishing ethics.

Requirements for articles design for publication in the journal are available on the websites:
www:nauka-nanrk.kz
ISSN 2518-1483 (Online), ISSN 2224-5227 (Print)
http://reports-science.kz/index.php/en/archive

Managing Editor: T. Apendiev
Editors: D.S. Alenov, A.Shormakova
Computer layout: G.D. Zhadyranova

Signed for print: June 22, 2026
Format: 70×90 1/16. 24.5 printed sheets. Order No. 2.

«Central Asian Academic Research Center» LLP
Almaty, Shevchenko Street, 28