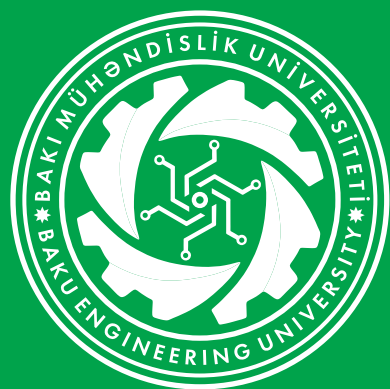




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SYNTHESIS AND STUDY OF THE ANTIBACTERIAL PROPERTIES OF CHOLIC ACID WITH GAMMA-AMINO ACIDS

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ARTICLE INFO	ABSTRACT
Article history: Received:2025-11-01 Received in revised form :2025-11-27 Accepted:2026-01-29 Available online:2026-06-26 Keywords: γ-aminobutyric acid, cholic acid, steroids, antibacterial activity.	Binding of choline acid to γ-amino acids allows complicate molecular structure and raise her pharmacological efficiency. Amino acids contain atoms nitrogen, which are playing important role in antimicrobial activities, so sow they capable interact with the cell membranes and enzymatic systems of microorganisms, disrupting their vital processes. Due to this, the synthesized compounds have a dual effect: bacteriostatic, when the growth of microorganisms is suppressed, and bactericidal, when their complete destruction is observed. The results of our research have shown that choline compounds with γ-amino acids demonstrate activity in narrow range concentrations, what is important indicator for pharmacological efficiency and follows for precise drug dosing. This opens the possibility of using such compounds as the basis for the creation of new antibacterial agents suitable for the prevention and treatment of mixed infections and infections resistant to traditional antibiotics. Furthermore, these compounds have the potential for complex action: they simultaneously protect liver function and effectively combat pathogenic microorganisms, making them particularly promising for use in hepatology and infectious diseases. Overall, the study of the antibacterial properties of cholic acid in combination with γ-amino acids Maybe become important step by step V development new therapeutic strategies, providing high efficiency at minimal side effects.

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1. INTRODUCTION

Steroid compounds occupy a special place in modern medicinal chemistry due to their pronounced biological activity, structural diversity, and ability to selectively influence a wide range of physiological processes. They are considered one of the most promising platforms for the creation of new therapeutic agents, including those intended for the treatment of diseases of the digestive and hepatobiliary systems. [1] The high biocompatibility of the steroid scaffold, its stability in biological environments, and the possibility of targeted modification make steroids convenient structural matrices for the development of pharmacologically active substances. In recent years, researchers have increasingly focused on naturally occurring steroids, particularly

bile acid derivatives, among which cholic acid occupies a key position. [2] It has pronounced amphiphilic properties, is bioavailable, and contains functional groups suitable for chemical transformations, which makes it possible to create a wide range of new compounds based on it. Modification of cholic acid opens up the possibility of obtaining substances with anti-inflammatory, antioxidant, antibacterial, cytoprotective, and immunomodulatory properties, which is especially relevant for the treatment of liver and gastrointestinal diseases [3]. For organic chemists and pharmacists, cholic acid is a convenient and well-studied substrate. The presence of reactive hydroxyl and carboxyl groups makes it possible to carry out a variety of esterification, acylation, amidation, reduction, and formation of complex biologically active fragments [4]. This allows for fine-tuning the lipophilicity, acid-base properties, spatial configuration, and biodistribution of the created compounds [5]. In parallel, the direction of designing steroid drugs capable of acting on specific cellular targets in the liver is developing, including FXR receptors, TGR5, and other elements of signaling pathways involved in the regulation of bile formation, lipid metabolism, and inflammatory processes. Such compounds are already demonstrating promising results in the treatment of cholestatic diseases, steatohepatitis, cirrhosis of various etiologies and intestinal diseases [6]. The binding of choline acid to γ -amino acids allows for a more complex molecular structure and increased pharmacological efficacy [7]. Amino acids contain nitrogen atoms, which play a key role in antimicrobial activity because they are capable of interacting with the cell membranes and enzymatic systems of microorganisms, disrupting their vital processes. This allows the synthesized compounds to have a dual effect: bacteriostatic, inhibiting microbial growth, and bactericidal, resulting in their complete destruction [8]. Our research demonstrated that choline compounds with γ -amino acids exhibit activity over a narrow concentration range, which is an important indicator of pharmacological efficacy and allows for precise drug dosing. This opens the possibility of using such compounds as the basis for the creation of new antibacterial agents suitable for the prevention and treatment of mixed infections and infections resistant to traditional antibiotics. Furthermore, these compounds have the potential for complex action: they simultaneously protect liver function and effectively combat pathogenic microorganisms, making them particularly promising for use in hepatology and infectious disease practice [9-16]. Overall, studying the antibacterial properties of cholic acid in combination with γ -amino acids could be an important step in the development of new therapeutic strategies that provide high efficacy with minimal side effects and a broad spectrum of action against microorganisms.

2. EXPERIMENTAL PART

Synthesis of γ -aminobutyric acid benzyl ester hydrochloride. The following method was used to obtain benzyl ester of γ -aminobutyric acid hydrochloride. 6 ml of thionyl chloride (SOCl_2) was added to a cooled solution.) 3 g (2.3372 g pure substance) of γ -aminobutyric acid were gradually added to 24 ml of absolute benzyl alcohol with constant, vigorous stirring using a magnetic stirrer. This step ensured complete wetting and partial dissolution of the initial precipitate, which facilitated a uniform reaction between the amino acid and SOCl_2 and the formation of intermediate products.

After thorough stirring, the reaction mixture was left at room temperature for 50 minutes, allowing the reaction to reach a significant degree of completion. Next, 100 ml of dry diethyl ether was added to liquefy and stabilize the reaction mixture. The mixture was cooled in a water

bath with ice and table salt, which facilitated the precipitation of benzyl γ -aminobutyrate hydrochloride as an amorphous precipitate. The precipitate was carefully filtered on a glass Schott filter and dried in a vacuum desiccator over granulated NaOH to remove residual moisture and acidic gases, which maintained the chemical stability of the product.

The described procedure yielded 1.5466 g of amorphous α -aminobutyric acid benzyl ester hydrochloride, representing a yield of 74.41% of the theoretical maximum. Thin-layer chromatography (TLC) was used to monitor purity and identify the product. These indicators confirm the stability and reproducibility of the synthesis, and the resulting hydrochloride is ready for further use in condensation reactions with epichlorohydrin and other stages of the synthesis of potentially biologically active compounds.

Synthesis of methyl ester hydrochloride γ -aminobutyric acid. To obtain crystalline benzyl ether hydrochloride γ -aminobutyric acid, the following method was used. 3 g of γ -aminobutyric acid, after which dry hydrogen chloride was passed through the resulting suspension without prior cooling. This step ensured complete dissolution of the amino acid and the formation of the hydrochloride salt in the alcohol solution, creating the basis for crystallization of the highly pure product.

After complete dissolution, the reaction mixture was carefully cooled in an ice-water bath, continuing to saturate with HCl at a temperature of 0–50°C. This facilitated a gentle crystallization process, preventing decomposition of the intermediate product and ensuring the formation of a proper crystal lattice.

To protect against moisture, the reaction mixture was passed through a calcium chloride tube and left overnight at room temperature to complete the reaction and stabilize the intermediate hydrochloride. The next day, the mixture was cooled again in an ice-salt water bath, which promoted the precipitation of crystalline hydrochloride. The precipitate was carefully filtered on a glass Schott filter and washed with cold benzyl alcohol and absolute diethyl ether to remove impurities. The resulting product was dried in a vacuum desiccator over granulated NaOH with the addition of absolute ether to remove all moisture and ensure crystal stability.

As a result of the described procedure, 2.7 g of crystalline benzyl ether hydrochloride were obtained. γ -aminobutyric acid, which corresponds to a yield of 77.14%. The resulting product was characterized by: Melting point: 211–213°C. These indicators confirm the high purity and crystalline nature of the compound, which makes it ready for further use in condensation reactions with epichlorohydrin and other stages of the synthesis of potentially biologically active derivatives.

Synthesis of 1-chloro-3-benzyl ether of α -bityryl propan-2-ol. A similar method used for the synthesis of α -aminobutyric esters was used to obtain this compound. The starting amounts were 0.54 g of epichlorohydrin and 1.5 g of benzyl γ -aminobutyrate hydrochloride. The reaction was carried out at a controlled temperature, allowing for the opening of the epichlorohydrin epoxide ring and the addition of γ -aminobutyric acid to the amine group, forming the glycidyl ester of propan-2-ol. The process proceeded without side reactions and yielded a stable, amorphous product. As a result of the reaction, 2.54 g of 1-chloro-3-benzyl ester of γ -aminobutyric acid propan-2-ol were obtained, which corresponds to a yield of 72.15% of the theoretically possible.

Thin-layer chromatography (TLC) was used to control purity and identification: The resulting amorphous product is ready for further use in the synthesis of glycerol and amino acid derivatives, and can also be used to study its biological activity and physicochemical properties.

Synthesis of 1-chloro-3-benzyl ether of γ -butyryl-propan-2-ol. Prepared using a similar method to 3., starting from 0.54 g of epichlorohydrin and 1.5 g of benzyl chlorohydrate of γ -aminobutyric acid. Obtained are 2.54 g (72.15%) of 1-chloro-3-benzyl ester of γ -aminobutyric acid of propan-2-ol in amorphous form, $R_f=0.56$ (A), $R_f=0.58$ (B).

1. Synthesis of 3 α ,7 α ,12 α -trihydroxycholanate-3- γ -aminobutyryl-propan-2-ol

A three-necked round-bottomed flask equipped with a reflux condenser, mechanical stirrer, and dropping funnel was charged with 1.09 g (0.01 mol) of 1-chloro-3-carbobenzoxy- γ -butyrylpropan-2-ol and 10 ml of absolute 1,4-dioxane. The reaction mixture was stirred for 6 hours at room temperature until the starting material was completely dissolved.

After complete dissolution, the reaction temperature was gradually raised to 75–80°C. Then, 0.75 ml (0.01 mol) of a solution of cholanolic acid salt in an appropriate solvent was added dropwise using a dropping funnel. After complete addition, the reaction mixture was stirred and heated for another 4–4.5 hours. The total reaction time was approximately 7 hours.

After the reaction was complete, the mixture was kept at room temperature for 16 hours. The solvent was removed by vacuum evaporation, yielding a white crystalline solid. The resulting product was purified by recrystallization from absolute benzene or isopropanol.

The yield of the target product was 1.8 g (86.7%). Melting point: 189–190°C.

Found, %:

C - 70.90; H - 11.70; N - 1.40; O - 16.01.

Calculated for C₅₉H₁₁₆NO₁₀, %:

C - 65.98; H - 11.05; N - 1.32; O - 15.12.

Thin layer chromatography data:

R_f = 0.61 (system A);

R_f = 0.59 (system B);

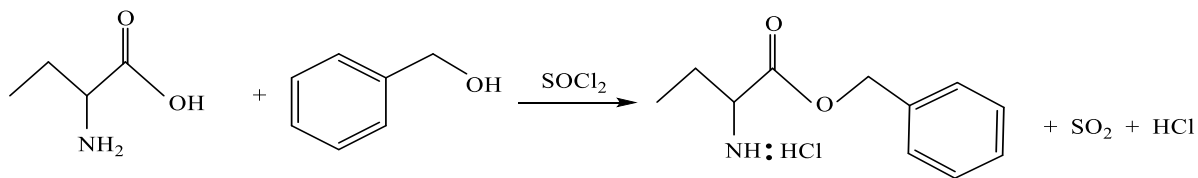
R_f = 0.56 (system B).

Iodomethylate vapor was used as a developer, which made it possible to visualize the spots of the compound being studied on chromatographic plates.

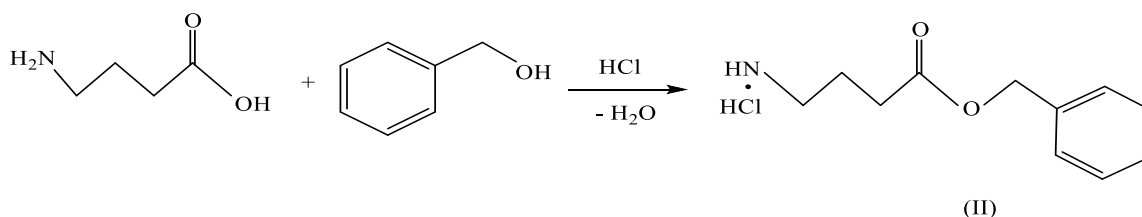
3. RESULTS AND DISCUSSION

For this study, we used α -aminobutyric acid (I) and γ -aminobutyric acid (II) benzyl ester hydrochlorides as starting compounds. We obtained these compounds using classical peptide chemistry methods, ensuring high purity and reproducibility of the products. The hydrochloride synthesis was carried out in several steps: first, α - and γ -aminobutyric acids were converted to the corresponding benzyl esters by esterification in the presence of an acid catalyst, after which the resulting esters were treated with hydrogen chloride to obtain the target hydrochloride compounds. All intermediate and final products were monitored using thin-layer chromatography (TLC) and IR spectroscopy to confirm their structure and purity.

The obtained hydrochlorides (I) and (II) served as key reagents in subsequent condensation reactions with epichlorohydrin and glycerol chlorohydrins, which made it possible to study the influence of the spatial arrangement of the amino group (α - or γ -position) on the reaction rate, the yield of the target product and the formation of side compounds.

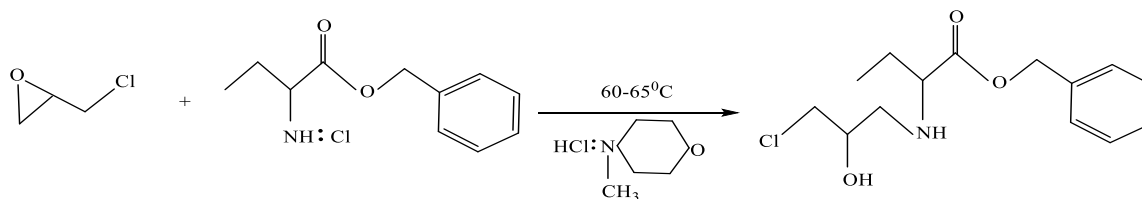


Benzyl γ -aminobutyrate hydrochloride was synthesized as follows: a solution of γ -aminobutyrate benzyl ester in anhydrous methanol was saturated with dry gaseous hydrogen chloride until the reaction mixture was completely absorbed. The process was carried out at a controlled temperature to ensure uniform formation of the hydrochloride and prevent decomposition of the starting ester. After completion of the reaction, the formed precipitate was filtered, washed with cold methanol to remove impurities and dried in a vacuum desiccator over granulated NaOH until a pure product was obtained. The process was carried out at a temperature of 0-50°C for 1-1.5 hours with constant stirring to ensure uniform interaction of the reagents. After completion of the reaction, the solution was left at a low temperature for crystallization of the product. The precipitated crystals of the hydrochloride were filtered, washed with cold dry ether to remove residual solvent and dried in a vacuum over P_2O_5 to constant mass.



The condensation reaction of synthesized α - and γ -aminobutyric acid benzyl ester hydrochlorides with epichlorohydrin was studied in absolute dioxane at 60–650°C. Experiments revealed that the reaction proceeds with high selectivity, forming stable condensation products without significant side reactions. The use of absolute dioxane ensured a homogeneous reaction medium and prevented epichlorohydrin hydrolysis, thereby maximizing the yield of the target compounds. The reaction was monitored using thin-layer chromatography, where the formation of new chromatographic bands corresponding to the condensation products was observed, while the starting hydrochlorides were completely separated.

The experiments conducted showed that the interactionThe reaction of benzyl α -aminobutyrate hydrochloride with epichlorohydrin produces a glycidyl ester. The reaction begins with the opening of the epoxide ring under the action of the amino group, leading to the formation of an active intermediate. Subsequently, a glycerol moiety attaches to the resulting epoxide center, resulting in the formation of a stable glycidyl ester. This process occurs at a controlled temperature of 60–650°C in an absolute dioxane environment, minimizing side reactions and yielding a highly purified product. The structure of the resulting compound was confirmed by thin-layer chromatography, IR spectroscopy, and elemental analysis, allowing for the reliably determination of the formation of the epoxide and glycerol moieties in the molecule.

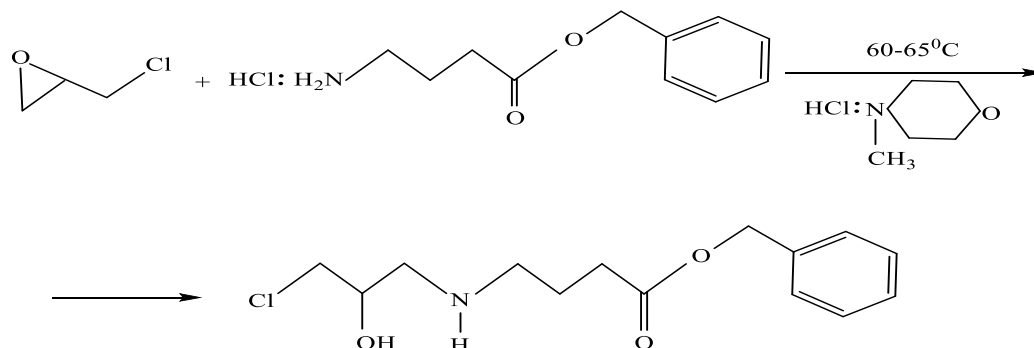


The structure of the synthesized products 4 and 5 was confirmed using a comprehensive spectral analysis, including ^1H NMR and ^{13}C NMR spectroscopy. Characteristic proton signals were identified in the ^1H NMR spectrum in methine and methylene groups, as well as for protons associated with the amino group and the epoxide fragment of the glycidyl ether. The singlet and multiplet signals allowed us to determine the positions of the substituents and confirm the preservation of the stereochemistry of the original amino acid residues.

^{13}C NMR analysis revealed the presence of all key carbonyl and aliphatic carbon atoms characteristic of glycidyl esters and benzyl esters of α - and γ -aminobutyric acid. The spectra revealed signals from the ester carbons, as well as those in the epoxide ring, confirming successful condensation with epichlorohydrin.

Comparison of the obtained data with published chemical shift values and proton integration ratios allowed for the reliable identification of products 4 and 5 and the exclusion of possible condensation byproducts. This approach ensures high accuracy of structure determination and confirms the validity of the synthetic scheme. A similar condensation reaction of epichlorohydrin with γ -aminobutyric acid benzyl ester hydrochloride was carried out. The reaction was carried out in absolute dioxane at a controlled temperature of 60–65°C to form the corresponding glycidyl ester. During the reaction, the nitrogen atom of the γ -aminobutyric acid amino group attacks epichlorohydrin, opening the epoxide ring and forming a new C–N bond while retaining the benzyl ester on the carboxyl group.

The resulting products were isolated using standard purification methods, including extraction and crystallization, after which their structure was confirmed by spectral analysis. ^1H NMR spectra revealed characteristic signals for the protons of the methylene and methine groups, as well as for protons associated with the amino group and glycidyl structure. ^{13}C NMR spectroscopy identified the carbonyl and aliphatic carbon atoms, including signals from the epoxide ring, confirming the successful completion of the reaction and the formation of the target product.



It has been experimentally established that under the influence of the amine group of γ -aminobutyric acid opens the epoxide ring of epichlorohydrin at a temperature of 60–650°C and a molar ratio of the reactants of 1:1 over a period of 3.5–4.0 hours. According to Krasusky's rule, described in the literature, the process proceeds with the preferential formation of propan-2-ol derivatives. The reaction mechanism involves the nucleophilic addition of the amine group to the less substituted carbon atom of the epoxide ring, which ensures the selective formation of the target product. During the reaction, the amine attacks the less sterically hindered carbon atom of the epoxide ring, leading to its opening and the formation of a new C–N compound while maintaining the carboxyl ester functional group.

The reaction progress and purity of the resulting compounds were monitored using thin-layer chromatography (TLC) on Sulufo plates.

Three eluent systems were used to separate the components:

1. **Chloroform-methanol (8:2)**– effective for isolating polar reaction products.
2. **n-Butanol–water–acetic acid (10:4:2)**– was used to separate hydrophilic compounds and amino acid fragments.
3. **Benzene-acetone-acetic acid (8:2:1)**– was used to evaluate non-polar and semi-polar components.

To visualize the chromatograms, iodine vapor was used as a developer, ensuring the appearance of distinct spots of all components. This approach allowed for rapid monitoring of reaction completion, identification of byproducts, and assessment of the purity of the synthesized compounds.

TLC analysis allowed us to identify the individuality of each compound obtained and to ensure the absence of by-products, ensuring control over the reaction progress. After confirming the structure and composition of the synthesized compounds (1–4) using elemental analysis and IR spectroscopy, the next stage of the research was carried out – studying the reaction of α -glycerol monochlorohydrin with these aminobutyric acids.

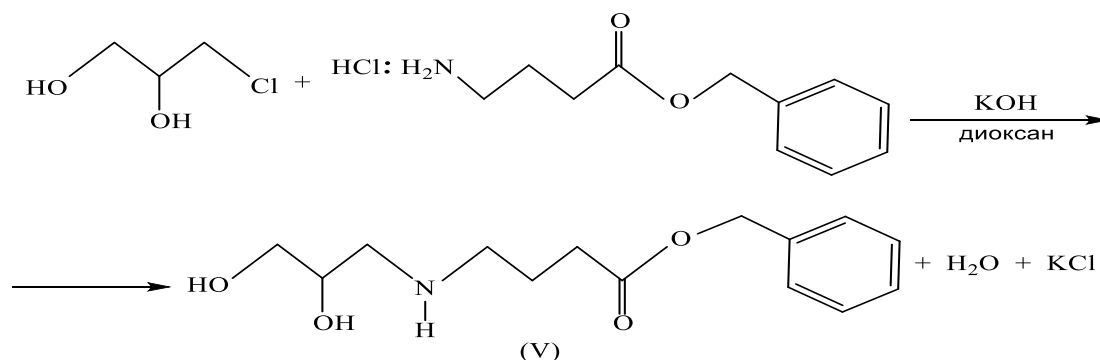
IR spectra of previously synthesized compounds showed characteristic bands:

- **760–820 cm^{-1}** – C–Cl stretching vibrations indicating the presence of organochlorine fragments,
- **1850–1965 cm^{-1}** – stretching vibrations of CH_2 and CH , confirming the preservation of the carbon chain,
- **1645 cm^{-1}** – stretching vibrations of C=O of the amide group (CO–NH), which confirms the formation of an amide bond,
- **3355–3375 cm^{-1}** – stretching vibrations of the hydroxyl group OH, indicating the presence of free hydroxyls that can participate in further reactions with glycerol.

These data indicated the correct formation of target products with an open epoxy ring and amine functionality.

In a subsequent study, glycerol α -monochlorohydrin was used in a reaction with benzyl esters of α - and γ -aminobutyric acids, enabling the study of the mechanisms of epoxide ring opening and the formation of new propan-2-ol compounds with potential biological activity. The reaction was

conducted under controlled conditions of temperature and molar ratio of the reactants, followed by analysis of the resulting products using thin-layer chromatography and IR spectroscopy to confirm the structure and purity of the compounds. The reaction was carried out under similar conditions—in absolute dioxane at 60–65°C with a controlled molar ratio of the reactants of 1:1. The results demonstrated high selectivity and the formation of glycidyl esters with preservation of the stereochemical structure, as confirmed by subsequent spectral and chromatographic analyses.



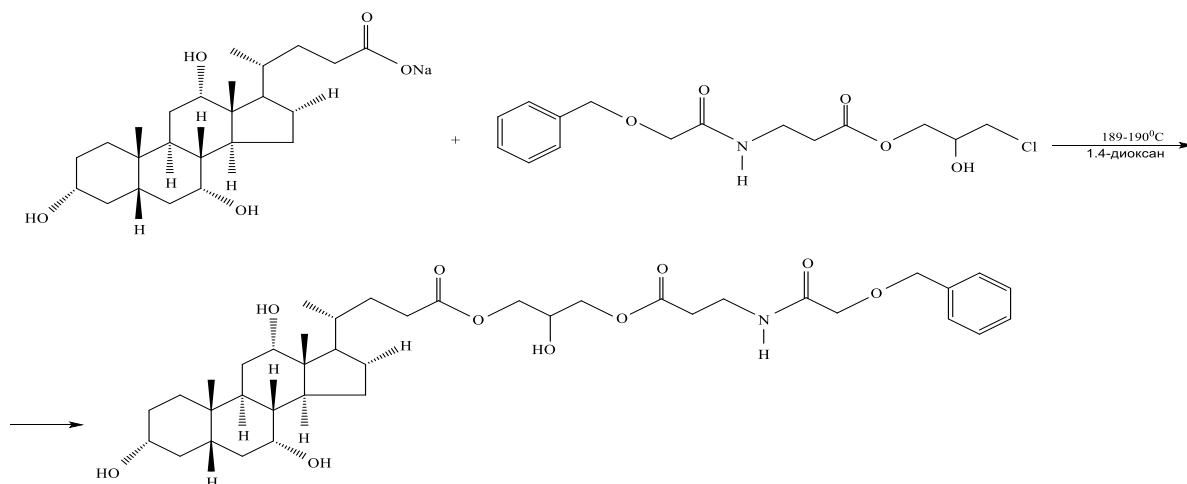
The reaction of α -monochlorohydrin glycerol with benzyl ester of γ -aminobutyric acid is carried out at a temperature of 60–65°C and a molar ratio of 1:1. The process proceeds through the opening of the epoxide ring of α -monochlorohydrin by the amine group of the ester, followed by the addition of a glycerol fragment, which leads to the formation of a glycidyl ester.

The reaction mechanism includes the following stages:

1. Nucleophilic attack of the amine group of γ -aminobutyric acid on the epoxide ring of glycerol monochlorohydrin.
2. Opening of the epoxy ring to form a secondary hydroxyl group.
3. Formation of a stable glycidyl ester with retention of amide and benzyl functionalities.

The synthesis of cholanolic acid derivatives with aromatic and aliphatic amino acids represents a promising direction in the development of new biologically active compounds with pronounced antifungal activity due to the presence of reactive functional groups. To obtain these compounds, an approach was used involving the interaction of amino acid esters and dipeptides with 2-chloromethyloxirane and cholanolic acid, which enabled the formation of new synthetic molecules with complex properties. Among the synthesized derivatives, compounds with multifaceted biological activity were observed, including antitumor, anti-inflammatory, antiviral, and antibacterial effects. Particular attention was paid to the bactericidal properties of the obtained compounds. Experimental evaluation was conducted on cultures of microorganisms of clinical and epizootic significance, such as *Staphylococcus aureus* (including saprophytic and epidermal strains), *Escherichia coli*, and *Salmonella*. The results showed that the compounds exhibited both bacteriostatic and bactericidal effects, depending on the microorganism species and drug concentration. These data demonstrate the potential of the developed compounds for the prevention and treatment of bacterial infections, as well as the possibility of reducing the development of pathogenic microbial resistance when using combination chemotherapeutic agents. An additional advantage is the ability to reduce the required drug dosage, which increases the cost-effectiveness of their use in human and veterinary practice.

For the first time, the study proposed drug screening among compounds structurally related to natural pyrimidines, such as thymine, uracil, and cytosine. This allowed for the identification of new avenues for the development of synthetic biologically active substances with predictable pharmacological activity.



The compound is a new compound not described in the literature, 3 α ,7 α ,12 α -trihydroxycho- lanate-3- γ -aminobutyryl-propan-2-ol, which belongs to the group of ester compounds.

Physicochemical constants are presented in Table 1.

No.	Name of the substance	Gross formula	Exit %	Tpl. 0C	R ^f *			%N	%Cl
					A	b	With		
1	Benzyl ether butanate hydrochloride	C ₆ H ₁₂ O ₂ NCl	74.42	Amorphous	0.31	0.37	0.51	27.45	26.69
								27.65	26.89
2	Benzyl ether hydrochloride-butanate	C ₁₁ H ₁₄ O ₂ N ₂ Cl	77.14	211-213	0.37	0.41	0.52	23.58	22.61
								23.88	22.91
3	1-chloro-3-benzyl ether butyropoan-2-ol	C ₉ H ₁₆ O ₃ NCl	76.12	Amorphous	0.62	0.71	0.67	23.31	23.31
								23.61	23.61
4	1-chloro-3-cabobenzoxy γ -butyrylpropan-2-ol	C ₂₅ H ₄₈ Cl NO ₅	81	120-121	0.56	0.58	0.65	24.62	23.53
								24.82	23.83
5	3 α ,7 α ,12 α -trihydroxycholanate-3- γ -aminobutyryl-propan-2-ol	C ₅₉ H ₁₁₆ NO ₁₀	86.7	189-190	0.63	0.68	0.70	24.72	23.63
								24.82	23.83

Study of biological activity. For the first time, the study proposed drug screening among compounds structurally related to natural pyrimidines, such as thymine, uracil, and cytosine. This allowed for the identification of new avenues for the development of synthetic biologically active substances with predictable pharmacological activity.

The antimicrobial activity of a specific compound, 3 α ,7 β -dihydroxycholic acid with gamma-amino acids, was assessed using serial dilutions in meat-peptone broth (MPB) against various epizootic and field strains of microorganisms: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Proteus vulgaris*, *Salmonella enteritidis*, *Salmonella pullorum*, *Pasteurella multocida*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*. For the experiment, a stock solution of 1-chloro-3-methyltryptophan-2-ol was prepared at a concentration of 5 mg per 100 ml of sterile purified water. Then, two-fold serial dilutions of the solution were performed in 2 ml MPB. Each ml of prepared media was supplemented with 200 μ l of a suspension of test microorganism cultures in isotonic sodium chloride solution, which enabled the precise

determination of minimum inhibitory concentrations of the drug for different strains. Thus, this study demonstrates the successful synthesis of new cholanolic acid derivatives with amino acid fragments and confirms their broad biological activity. The obtained data open up prospects for further study of these compounds as potential antifungal, antibacterial, and antiviral agents, as well as for the development of complex chemotherapeutic agents with improved pharmacological properties.

Microorganism samples were incubated under strictly controlled conditions at 37°C for 24–48 hours, allowing for accurate assessment of culture growth and the effect of the synthesized compound 3 α ,7 β -dihydroxycholic acid with gamma-amino acids on them. Incubation was performed using optimal conditions for each bacterial species to eliminate the influence of external factors on microbial activity and reliably determine the pharmacological potential of the test substance. After the incubation period, bacterial growth was quantified and the minimum bacteriostatic concentration (MBC) was determined. This is the concentration of the substance at which inhibition of microbial growth and reproduction is observed, which serves as a criterion for its effectiveness as a bacteriostatic agent.

To more accurately determine the minimum bactericidal concentration (MBC), repeat experiments were conducted on meat-peptone agar (MPA), which serves as an indicator of microbial death. The absence of growth on MPA indicates complete cell destruction, allowing one to distinguish bactericidal action from a purely bacteriostatic one. These tests also used positive and negative controls on MPA and MPA, ensuring the reliability of the results and distinguishing the effect of the test compound from the possible influence of the incubation medium or natural fluctuations in microbial growth. Experimental data demonstrated that the synthesized 3 α ,7 β -dihydroxycholic acid with gamma-amino acids exhibits high activity against a wide range of microorganisms, including pathogenic and opportunistic strains: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pasteurella multocida*, *Proteus vulgaris*, *Salmonella enteritidis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella pullorum*, and *Klebsiella pneumoniae*. For these strains, MBC concentrations ranged from 0.33 to 1.26 $\mu\text{g/ml}$, indicating the substance's high efficacy in suppressing bacterial growth. Analysis of the results also revealed that different microorganisms exhibit varying sensitivity, which is important for determining the compound's spectrum of activity and planning its practical application. The stability of the synthesized substance was additionally assessed. Experiments have shown that 3 α ,7 β -dihydroxycholic acid with gamma-amino acids retains bactericidal activity over a wide concentration range—from 0.54 to 3.96 $\mu\text{g/ml}$ —and exhibits high thermal stability, confirming its suitability for use in various pharmaceutical formulations. These characteristics are important for the development of drugs with a long shelf life and predictable therapeutic effect, as well as for use under variable external factors, such as changes in temperature or environmental composition. The practical significance of the obtained data lies in confirming that the synthesized compound is capable of acting as an effective antimicrobial agent against a wide range of pathogenic microorganisms. The low MBC range and high stability of the substance allow its use in pharmacological preparations for the prevention and treatment of bacterial and mixed infections, reducing the risk of pathogenic microorganism resistance. Furthermore, effective action at relatively low doses may reduce the need for increased therapeutic dosages, improving the safety and cost-effectiveness of the drug. Thus, the studies conducted confirm the high efficacy and stability of 3 α ,7 β -dihydroxycholic acid with gamma-amino acids, demonstrating its potential for further clinical study as a broad-spectrum antimicrobial and antifungal agent. These tables reflect

the ranges of the minimum bacteriostatic concentration (MBc) and minimum bactericidal concentration (MBC) of the synthesized compound 3 α ,7 β -dihydroxycholic acid with gamma-amino acids against various microorganisms. These data demonstrate that the synthesized compound has a broad spectrum of antimicrobial activity. Gram-positive bacteria (St. aureus, Str. pyogenes) are most sensitive to it, while gram-negative microorganisms (E. coli, S. pullorum, Kl. pneumoniae) require higher concentrations to achieve a bacteriostatic and bactericidal effect. The overall range of MBcK and MBC confirms the efficacy of the compound in pharmacological applications and its potential for the development of broad-spectrum anti-infective drugs.

Table 2. Antibacterial activity 3 α ,7 β -dihydroxy cholevaya acids With gamma-amino acids,mcg/ml

Microorganism	MBsK	MBsK
St. aureus	0.29 – 1.19	0.55 – 2.66
Str. Pyogenes	0.44 – 1.14	0.77 – 2.55
E. coli	1.22 – 4.55	2.42 – 9.03
Pr. Vulgaris	0.58 – 2.65	1.32 – 4.54
S. enteritidis	0.55 – 2.66	1.33 – 4.88
S. pullorum	1.32 – 4.77	2.33 – 9.78
P. multocida	0.77 – 1.44	0.55 – 2.77
Ps. Aeruginosa	0.65 – 2.65	1.33 – 4.55
Kl. Pneumonia	1.33 – 4.77	2.55 – 9.88

3 α ,7 β -dihydroxycholic acid with aminobutyric acid derivatives exhibits pronounced antimicrobial activity against a wide range of microorganisms, including epizootic strains and laboratory cultures used in control studies. This compound has the ability to inhibit bacterial growth in the concentration range of 0.72–9.22 μ g/ml, indicating its high biological efficacy. Experimental studies have shown that this substance has both bacteriostatic and bactericidal effects. In particular, at the lower end of the concentration range (approximately 0.72 μ g/ml), a slowdown in microorganism growth was observed, reflecting a bacteriostatic effect, and at higher concentrations (up to 9.22 μ g/ml), complete cessation of growth and cell death of microorganisms were observed, indicating bactericidal activity. In addition, the compound exhibits high efficacy against strains obtained from field conditions, which is especially important for epizootic and clinical studies. A comparison of the results with laboratory strains showed that 3 α ,7 β -dihydroxycholic acid with gamma-amino acids exhibits a more pronounced bactericidal effect on field strains, indicating its potential for use in veterinary and clinical practice to combat bacterial infections. The compound's mechanism of action is likely related to the interaction of the molecule's functional groups with bacterial cell membranes, disrupting their integrity and inhibiting key enzymatic processes. The compound's high activity is also explained by the presence of hydroxyl groups 3 α and 7 β , which enhance the molecule's polarity and increase its ability to interact with microbial membrane structures. The obtained data highlight the practical significance of the compound as a potential broad-spectrum antimicrobial agent capable of effectively inhibiting the growth of both laboratory and field strains of microorganisms. This makes it a promising candidate for further study as a pharmacological agent for the prevention and treatment of bacterial infections in veterinary and human medicine.

4. CONCLUSIONS

As a result of the research, six new compounds belonging to the class of propan-2-ols and propane-1,2-diols, previously undescribed in the scientific literature, were synthesized, isolated, and characterized in detail. These compounds are derivatives of α - and γ -aminobutyric acid condensed with epichlorohydrin and glycerol mono- or dichlorohydrin, forming a unique combination of hydroxyl and amino groups in the molecule. The structure of the obtained compounds was confirmed using IR spectroscopy and elemental analysis, which allowed for the identification of key functional groups, including hydroxyl ($-\text{OH}$), amide ($-\text{CO}-\text{NH}$), and chlorine-containing ($-\text{C}-\text{Cl}$) moieties. Purity and reaction progress were monitored using thin-layer chromatography, using various eluent and developer systems, ensuring high reliability of the obtained data. Each of the isolated compounds was subjected to comprehensive spectroscopic analysis, including IR spectroscopy and H and C NMR, as well as elemental analysis to confirm composition and structure. The IR spectra revealed characteristic absorption bands confirming the presence of hydroxyl groups, amino groups, and carbonyl moieties, while NMR spectra allowed the arrangement of substituents within the carbon skeleton to be determined and the structure of the propan-2-ols and propane-1,2-diols to be confirmed.

These new compounds exhibit high chemical stability and purity, making them promising for further study as potentially biologically active molecules. The isolation of these previously undescribed derivatives opens up opportunities for the development of new drugs and for in-depth studies of the reactivity of propane-2-ols and propane-1,2-diols in organic and pharmaceutical chemistry.

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SYNTHESIS OF ACETYLENIC ALCOHOLS BASED ON CYCLOPROPYLACETYLENE AND AROMATIC ALDEHYDES AND THEIR MOLECULAR DOCKING ANALYSIS AGAINST THE NOX2 RECEPTOR

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ARTICLE INFO	ABSTRACT
Article history: Received:2025-11-23 Received in revised form: 2025-12-15 Accepted: 2026-01-18 Available online:2026-06-26 Keywords: acetylenic alcohols, benzaldehyde, alkynylation reactions, catalytic system, enantioselective, Grignard reagent, reaction mechanism	In this research work, the nucleophilic addition reaction of cyclopropylacetylene with aromatic aldehydes was investigated in the presence of a catalytic system consisting of EtMgCl/C₁₇H₂₉NO/TFE. Within the scope of the study, the reactivity of benzaldehyde derivatives containing various functional groups (fluoro, chloro, bromo, alkyl, alkoxy, and hydroxyl) as well as structurally complex anthracene-9-carbaldehyde substrates was analyzed. The proposed synthetic method does not require expensive metals as catalysts or ultra-low temperatures. This methodology is considered cost-effective and convenient, enabling the preparation of structurally diverse acetylenic alcohols with high chemical yields (up to 91%). During the process, the primary factors influencing product yield and selectivity such as the composition of the catalytic system, stoichiometric ratios of the reagents, temperature, and reaction duration were systematically studied. It was demonstrated that 2,2,2-trifluoroethanol (TFE) serves to break down magnesium acetylide associates, thereby enhancing the reactivity of the in situ formed complex. A reaction mechanism for the alkynylation reaction, based on the cooperative effect of the ligand and the fluorine-containing components, was proposed. The electronic and steric effects of the substituents within the aldehydes were explained based on chemical principles. The structures and purity of the synthesized compounds were confirmed using ¹H, ¹³C NMR spectroscopy.

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1. INTRODUCTION

Aromatic acetylenic alcohols represent an important class of organic compounds containing an aromatic ring, an acetylenic (C≡C) bond, and a hydroxyl group within a single molecule. These compounds are widely utilized in the pharmaceutical industry, polymer chemistry, the synthesis of biologically active substances, and materials science [1-5].

In recent years, catalytic systems based on *ProPhenol* ligands and Me_2Zn have demonstrated high efficiency in the synthesis of aromatic acetylenic alcohols. The alkynylation reaction of heteroatom-containing aldehydes with phenylacetylene has been investigated using the *ProPhenol*/ Me_2Zn catalytic system. As part of the research, the effects of reaction duration and temperature on product yield were systematically analyzed, and optimal reaction parameters were determined. Furthermore, the authors conducted a comparative study of the reactivity of various heteroatom-containing aldehydes, determining the influence of electronic and steric effects on reaction capability and product yield [6].

In the nucleophilic addition reaction of benzaldehyde and its halogenated derivatives with phenylacetylene, a complex catalytic system based on $\text{Zn}(\text{OTf})_2$ and $\text{TBAF} \cdot 3\text{H}_2\text{O}$ was employed. The influence of benzaldehyde and its halogen substituents on product yield was comprehensively analyzed. A reaction mechanism was proposed, and the reaction stages, activation energies, and kinetic characteristics were determined. Based on the selected catalytic system, relative efficiency series for the synthesis of aromatic acetylenic alcohols were proposed [7].

Lucke and his research group were the first to employ palladium complexes based on sydnones and sydnone imines in Sonogashira-Hagihara and Buchwald-Hartwig cross-coupling reactions. In this study, seven different Pd complexes were synthesized and their catalytic activities were investigated. The most effective results were achieved using the $[\text{sydnone-4-yl-PdBr}(\text{PPh}_3)_2]$ complex, which provided a 100% yield in the reaction between phenyl bromide and 2-methylbut-3-yn-2-ol within 7 hours. It was highlighted that this result demonstrates shorter reaction times and higher efficiency when compared to the well-known $\text{Pd}(\text{PhCN})_2\text{Cl}_2/\text{CuI}/\text{P}(\text{t-Bu})_3$ catalytic system reported in the literature. In the study, ten different aromatic and heterocyclic acetylenic alcohols were synthesized, with thiophene, quinoline, phenanthrene, and anthracene derivatives obtained in high yields. The authors noted that although palladium complexes of sydnone imine derivatives required longer reaction times, they provided the best results for naphthalene derivatives [8].

New methods for the synthesis of vinyl ethers via modification of aromatic and aliphatic alkynes and acetylenic alcohols containing a triple bond have been developed [9], as well as new approaches for the synthesis of α -acrylamides based on nickel-catalyzed hydroalumination and nucleophilic addition reactions with isocyanates. This method allows for the efficient modification of both terminal and internal alkynes. The authors synthesized over 30 compounds with yields ranging from 70% to 98%. The reaction was conducted at 60°C for 2 hours, with substrate and reagent quantities optimized based on resource-efficiency principles. It was emphasized that this method requires lower temperatures and shorter reaction times compared to traditional Pd-catalyzed hydroamidation processes [10].

Ethynylation reactions of carbonyl compounds (aldehydes and ketones), imines, ketoesters, ketamine esters, oxycarbenes, and aldimines with various alkynes and their heteroatom derivatives have been studied in catalytic systems prepared on the basis of heavy metal (Zn, Au, Ag, Cu, Ti) salts and strong Lewis acids, and methods for the synthesis of new organic compounds have been developed [11-20].

2. RESULTS AND DISCUSSION

In this study, a series of *R*-substituted benzaldehyde derivatives containing alkyl, alkoxy, hydroxyl and halogen groups were selected. The alkynylation reactions were carried out with cyclopropylacetylene using the EtMgCl/C₁₇H₂₉NO/TFE catalytic system, resulting in the synthesis of the corresponding aromatic acetylenic alcohols (1-15). Reaction mechanisms for the synthesis of acetylene alcohols. The reaction was efficiently promoted by the EtMgCl/C₁₇H₂₉NO/TFE catalytic system at room temperature. The substrate scope utilized for this study included: Unsubstituted and alkyl-substituted benzaldehydes: Benzaldehyde and 4-ethylbenzaldehyde. Halogenated benzaldehydes - various isomers of fluoro- (2-F, 3-F, 4-F) and chloro-benzaldehydes (2-Cl, 3-Cl, 4-Cl), along with 3-(trifluoromethyl)benzaldehyde. Oxygenated and functionalized benzaldehydes - 4-butoxy-3-methylbenzaldehyde, 4-hydroxy-3-methylbenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 2-bromo-4,5-dimethoxybenzaldehyde and 3,4-dihydroxy-5-methoxybenzaldehyde. Polycyclic aldehydes - anthracene-9-carbaldehyde.

Based on established literature sources [21-26], the reaction mechanism is proposed to involve the formation of a magnesium acetylide intermediate, which subsequently undergoes coordinated addition to the carbonyl group, stabilized by the synergistic effect of the chiral ligand and the trifluoroethanol (TFE) additive. The reaction scheme was proposed as follows:

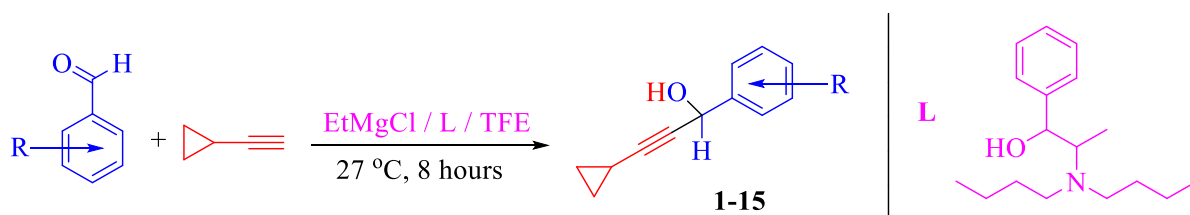
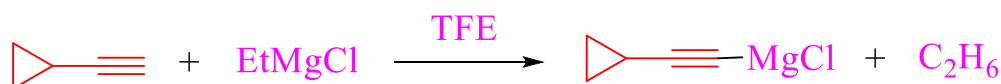


Fig. 1. General reaction scheme for the synthesis of aromatic acetylenic alcohols

Alkynylation reactions are proposed to occur through the following steps [27-29]. The catalytic process initiates with the in situ deprotonation of cyclopropyl acetylene to generate the active nucleophilic reagent. This preliminary stage involves the interaction of the terminal alkyne with EtMgCl in the presence of trifluoroethanol.

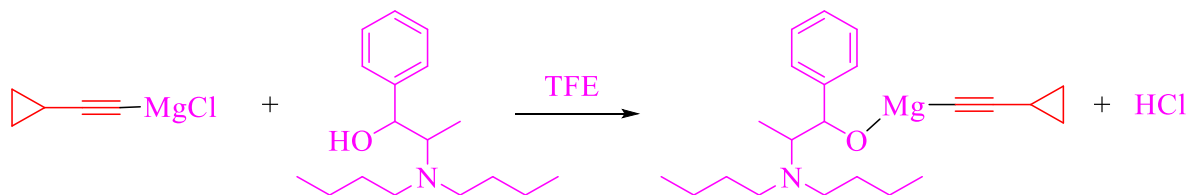
The ethyl group of the Grignard reagent acts as a strong base, deprotonating the acidic proton at the terminal position of the cyclopropyl acetylene. The subsequent evolution of ethane gas resulting from this acid-base interaction serves as the primary thermodynamic driving force, shifting the equilibrium toward the formation of the product. Consequently, a highly reactive intermediate, cyclopropylethynylmagnesium chloride, is successfully formed.



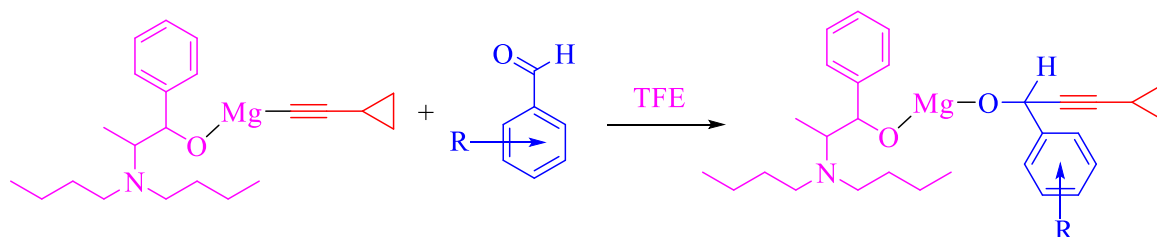
In the subsequent stage of the reaction, the coordination of the previously formed cyclopropylethynylmagnesium chloride intermediate with the chiral ligand is observed. The cyclopropylethynylmagnesium chloride establishes a coordination bond with the oxygen atom of the chiral ligand.

This complex chemical process leads to the formation of a cyclopropylethynylmagnesium alcoholate coordinated with both the chiral ligand and trifluoroethanol, accompanied by the elimination of hydrogen chloride from the system. This chiral complex serves as the primary

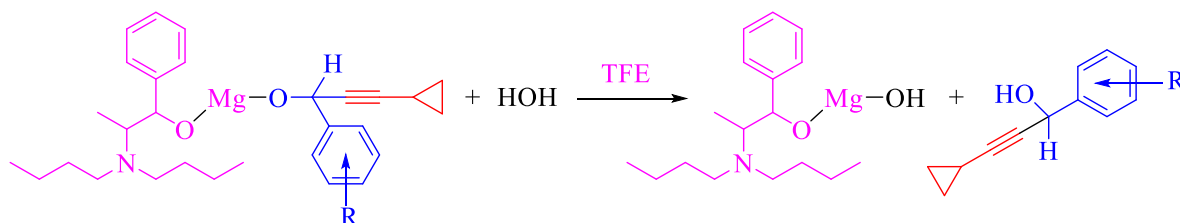
active catalytic species responsible for ensuring the enantioselective attack on the carbonyl group of the aldehyde in the following step.



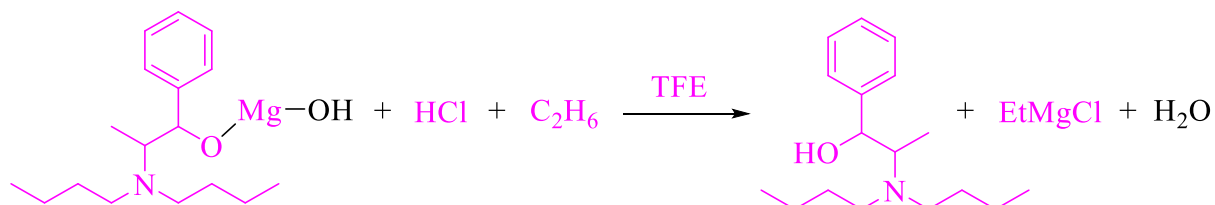
In the next step, the chiral magnesium alcoholate complex reacts with the aldehyde to form the new C-C bond. The carbonyl oxygen coordinates to the magnesium center, which triggers a significant increase in the electrophilicity of the carbonyl carbon. This activation makes the carbon atom highly susceptible to nucleophilic attack, effectively driving the reaction forward.



In the final stage, hydrolysis of the magnesium alcoholate intermediate leads to the cleavage of the magnesium oxygen (Mg-O) bond, followed by protonation. This process yields the target asymmetric propargyl alcohol and the magnesium hydroxide complex (L-Mg-OH). The liberation of the free alcohol effectively completes the catalytic cycle, allowing for the isolation of the chiral product in high optical purity.



The reaction concludes with the formation of a magnesium hydroxide species (Mg-OH) and the recovery of the chiral ligand. This stage ensures the straightforward separation of the catalyst from the system and facilitates the final work-up procedure.



The overall process enables the regeneration of the catalyst and ensures the isolation of the final product with high optical purity. The alkynylation of aromatic aldehydes in the selected catalytic system was investigated within a temperature range of 10 to 40 °C for 4-12 hours. To qualitatively and quantitatively evaluate the influence of key parameters-such as temperature, reaction time, and reagent ratios on the process and product yield, a mathematical model was developed.

Optimization was conducted using the Box-Wilson method [30-31], which allowed for the determination of ideal conditions for achieving maximum yields. Based on experimental research results, it was established that the product is synthesized in high yields when the reaction is carried out for 8 hours at 25 ± 2 °C, using the selected substrate, reagent, catalyst, and ligand (aldehyde:alkyne:EtMgCl:L) in a molar ratio of 1:1.2:1.2:0.2 respectively.

Furthermore, the formation of intermediate and by-products was monitored to understand their impact on the reaction pathway. Some specific values of the synthesized acetylene alcohols were determined and the results obtained are presented in table 1.

Table 1. Physicochemical characteristics of the synthesized aromatic acetylenic alcohols

Nº	Gross formula	Molecular mass, g/mol	Product yield	System	R _f value
1	C ₁₂ H ₁₂ O	172	89.1	Hexane:EtOAc 10:1	14/37
2	C ₁₄ H ₁₆ O	200	84.3	Hexane:EtOAc 10:1	18/37
3	C ₁₂ H ₁₁ OF	190	88.2	Hexane:EtOAc 14:1	14/38
4	C ₁₂ H ₁₁ OF	190	91.0	Hexane:EtOAc 14:1	17/38
5	C ₁₂ H ₁₁ OF	190	85.3	Hexane:EtOAc 14:1	20/37
6	C ₁₃ H ₁₁ OF ₃	240	86.5	Hexane:EtOAc 14:1	17/37
7	C ₁₂ H ₁₁ OCl	207	86.8	Hexane:EtOAc 14:1	14/37
8	C ₁₂ H ₁₁ OCl	207	89.3	Hexane:EtOAc 14:1	15/38
9	C ₁₂ H ₁₁ OCl	207	85.7	Hexane:EtOAc 14:1	12/38
10	C ₁₇ H ₂₂ O	258	88.1	Hexane:CH ₂ Cl ₂ 14:1	12/34
11	C ₁₄ H ₁₆ O ₂	216	86.4	Hexane:CH ₂ Cl ₂ 14:1	17/37
12	C ₁₅ H ₁₈ O ₄	262	88.3	Hexane:CH ₂ Cl ₂ 14:1	16/37
13	C ₁₄ H ₁₅ O ₃ Br	311	84.0	Hexane:CH ₂ Cl ₂ 14:1	15/37
14	C ₁₃ H ₁₄ O ₄	234	82.3	Hexane:EtOAc 6:1	12/37
15	C ₂₀ H ₁₆ O	272	84.7	Hexane:EtOAc 6:1	15/37

Based on the data presented in the table, it can be noted that aromatic acetylenic alcohols containing various electron-donating and electron-acceptor substituents on the aromatic ring were synthesized from the corresponding aldehydes with yields ranging from 83% to 91%. It is particularly important to highlight that compounds 3, 4, and 5 have the same gross formula and are ortho-, meta- and para-isomers containing a fluorine atom as the substituent.

The difference in the yield among these isomers can be explained by considering mesomeric and inductive effects, along with the spatial hindrance created by the substituent. Thus, the nature and position of substituents on the aromatic aldehyde significantly affect the product yield. In

this case, when electron-acceptor groups (F, Cl) are in the para-position, the nucleophilic attack of the alkyne on the carbonyl group is facilitated due to the increased electrophilicity of the carbonyl carbon atom, thereby ensuring the synthesis of the target acetylenic alcohols in high yields (90-91%).

Conversely, substituents in the ortho-position create steric hindrance, which leads to a decrease in product yield (83-85%). The structural identities of the resulting aromatic acetylenic alcohols were confirmed by spectroscopic methods.

The quantum chemical properties of the synthesized aromatic acetylenic alcohols were calculated using modern software.

Table 2. Results of quantum chemical calculations of synthesized aromatic acetylenic alcohols

Aromatic acetylene alcohols	Thermal energy, kcal/mol	Van der Waals energy, kcal/mol	Clone energy, kcal/mol	Torsion energy, kcal/mol	Valence angle energy, kcal/mol	Bond energy, kcal/mol
1	4.5147	6.0312	0.2554	-3.1905	0.388	1.2859
2	5.0340	4.6142	0.9875	-3.9569	0.5293	2.8599
3	0.0921	2.3387	-0.8067	-3.2518	0.2786	1.5332
4	3.2833	2.9637	1.3050	-3.1351	0.2874	1.8622
5	3.2491	2.9955	1.2681	-3.1279	0.2822	1.8313
6	8.8165	3.9246	1.3850	0.7888	0.416	2.3022
7	-0.4868	0.1116	-0.0390	-2.9379	0.4655	1.9132
8	2.4977	2.9276	0.9284	-3.2152	0.2862	1.5708
9	2.6468	3.0885	0.8892	-3.2089	0.2881	1.5899
10	11.9322	7.7509	1.1262	-2.6518	0.9692	4.7378
11	8.4417	5.5218	0.5748	-1.0785	0.6706	2.7530
12	21.6591	9.6203	0.7419	4.1066	1.5103	5.6800
13	13.4099	7.1512	-0.3697	0.1108	1.0848	5.4339
14	-3.7365	-2.1157	-2.1653	-6.0052	6.661	5.8887
15	1.2286	15.602	0.8156	-21.1261	1.7476	4.1893

Table 2 presents the calculated molecular mechanics and energy parameters for compounds 1-15. These parameters were investigated to evaluate the conformational stability and potential spatial interactions of the synthesized aromatic acetylenic alcohols. The obtained values represent the intramolecular strain occurring during structural rearrangements. In particular, compound 15 possesses a high negative torsion energy and a significant Van der Waals contribution due to its stable anthracene core. These quantum chemical values correlate well with the geometric complementarity and binding strength observed in the molecular docking studies against the active site of the receptor.

Molecular docking. The molecular docking method is an essential tool in contemporary pharmaceutical research for examining the interactions between biologically active substances and their target proteins. This method makes it possible to assess a ligands thermodynamic stability and capacity for binding to the protein. The stability of the ligand-protein complex is reflected in the binding free energy ($\Delta G_{\text{binding}}$) determined by docking software; the stronger the binding interaction, the more negative the value [32].

Table 3. Binding energies of the synthesized aromatic acetylenic alcohols with the 7U8G structure of the core human NADPH oxidase NOX2

With a value of -8.2 kcal/mol, compound 15 displayed the lowest binding energy among the synthesized compounds with the 7U8G (NOX2) receptor. This outcome suggests that with NOX2, this molecule can create the most energetically favorable and stable complex. Among the high-affinity ligands are also compound 6 (-8.1 kcal/mol) and compound 10 (-7.3 kcal/mol). Their binding energies demonstrate strong affinity and excellent structural complementarity within the target active cavity. By contrast, compound 13 displayed the lowest binding with the 7U8G receptor at -6.7 kcal/mol. This value indicates fewer interactions between the ligand and the receptor since it is much higher than those of the other compounds.

Fig. 2. Comparison of molecular docking poses and 2D interaction diagrams of the highest-scoring compound (15) and the lowest-scoring compound (13) within the active site of the core human NADPH oxidase NOX2 (PDB ID: 7U8G)

interactions within the active site of the protein are mainly restricted to spatial constraints and alkyl contacts of the cyclopropyl ring, the aromatic core, and the bromine atom of the molecule with Leu60, Leu219, Ala57, His115, His222, and His119 residues, indicating that the ligand could not achieve an energetically favorable orientation within the active site of the protein. The high binding affinity of compound 15 correlates well with its geometric and electronic properties. According to the quantum chemical calculations, this compound demonstrated the highest Van der Waals energy (15.60 kcal/mol) and a significant negative torsion energy (-21.12 kcal/mol). These parameters ensure the conformational stability of the ligand and its effective spatial interaction with specific hydrophobic regions of the protein. The complex and bulky structure of the anthracene fragment not only promotes a stable complex formation within the active site of the protein but also facilitates the transition of the molecule into an energetically favorable conformation. Furthermore, the synthesis of compound 15 with a high yield demonstrates a correlation between its chemical reactivity and biological activity potential.

3. EXPERIMENTAL PARTS

IR spectra were recorded on a Perkin-Elmer Spectrum 2000 FT-IR spectrometer using KBr pellets. ^1H NMR (400 MHz) spectra were recorded on a Bruker AMX spectrometer using CDCl_3 or C_6D_{12} as solvents, with TMS or GMS as internal standards (δ -scale). Solvents were evaporated using Heidolph Hei-VAP Core and Expert rotary evaporators. Crude products were purified by flash or column chromatography on silica gel 60, employing various organic solvents as eluents. The progress of the reactions and product purity were monitored by thin-layer chromatography (TLC).

Synthesis of 3-cyclopropyl-1-phenylpropyn-2-ol-1 using the $\text{EtMgCl}/\text{C}_{17}\text{H}_{29}\text{NO}/\text{TFE}$ catalytic system (1): A 50 mL dry vial equipped with a magnetic stir bar was charged with 10 mL of 2,2,2-trifluoroethanol (TFE). To this solution, ethylmagnesium chloride (1.07 g, 12 mmol) and cyclopropylacetylene (0.79 g, 12 mmol) were added sequentially. The mixture was stirred for 60 min at room temperature to facilitate the formation of the magnesium acetylide intermediate. Subsequently, the chiral ligand 2-(dibutylamino)-1-phenylpropan-1-ol (0.53 g, 2 mmol) and benzaldehyde (1.06 g, 10 mmol) were added, followed by a catalytic amount of hydroquinone to prevent polymerization. The reaction mixture was stirred for 8 hours at ambient temperature. Upon completion, the mixture was quenched with water and stirred for an additional 3 hours to ensure complete hydrolysis. The crude product was extracted with dichloromethane (3×10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4 . The solvents were removed under reduced pressure by simple distillation. The resulting residue was further purified by column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (10:1) as the eluent to afford the pure product 3-cyclopropyl-1-phenylprop-2-yn-1-ol (1) in 89.1 % (1.53 g) yield.

The remaining aromatic acetylenic alcohols were synthesized according to this general procedure. The ^1H NMR spectra confirming the structures of the synthesized compounds and their structural formulas are presented below.

3-cyclopropyl-1-phenylprop-2-yn-1-ol (1). ^1H NMR (400 MHz, CDCl_3) δ 7.48-7.23 (m, 5H, Ar-H), 5.78-5.52 (m, 2H, CH-OH and OH), 2.68 (td, $J=7.0, 2.5$ Hz, 1H, CH-cyclopropyl), 1.55-1.33 (m, 4H, cyclopropyl).

3-cyclopropyl-1-(4-ethylphenyl)prop-2-yn-1-ol (**2**). ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.26 (m, 2H), 7.19 (dt, $J=7.5$, 1.0 Hz, 2H), 5.73-5.44 (m, 2H), 2.75-2.55 (m, 3H), 1.45 (dd, $J=7.1$, 2.4 Hz, 4H), 1.23 (t, $J=8.0$ Hz, 3H).

3-cyclopropyl-1-(2-fluorophenyl)prop-2-yn-1-ol (**3**). ^1H NMR (400 MHz, CDCl_3) δ 7.53-7.27 (m, 2H), 7.27-7.16 (m, 2H), 5.84 (dd, $J=6.7$, 2.5 Hz, 1H), 5.64 (d, $J=6.8$ Hz, 1H), 2.65 (pd, $J=7.1$, 2.6 Hz, 1H), 1.53-1.34 (m, 4H).

3-cyclopropyl-1-(3-fluorophenyl)prop-2-yn-1-ol (**4**). ^1H NMR (400 MHz, CDCl_3) δ 7.39 (td, $J=7.5$, 5.0 Hz, 1H), 7.23 (ddt, $J=22.4$, 7.9, 1.5 Hz, 2H), 7.01 (tt, $J=7.8$, 1.6 Hz, 1H), 5.72 (d, $J=6.7$ Hz, 1H), 5.61 (dd, $J=6.7$, 2.5 Hz, 1H), 2.67 (pd, $J=7.1$, 2.6 Hz, 1H), 1.53-1.28 (m, 4H).

3-cyclopropyl-1-(4-fluorophenyl)prop-2-yn-1-ol (**5**). ^1H NMR (400 MHz, CDCl_3) δ 7.68-7.56 (m, 2H), 7.33-7.22 (m, 2H), 5.84 (d, $J=6.7$ Hz, 1H), 5.78 (dd, $J=6.7$, 2.5 Hz, 1H), 2.84 (pd, $J=7.1$, 2.5 Hz, 1H), 1.69-1.46 (m, 4H).

3-cyclopropyl-1-(3-(trifluoromethyl)phenyl)prop-2-yn-1-ol (**6**). ^1H NMR (400 MHz, CDCl_3) δ 7.59 (t, $J=1.4$ Hz, 1H), 7.49 (dt, $J=7.5$, 1.6 Hz, 1H), 7.30 (t, $J=7.5$ Hz, 1H), 7.21 (dt, $J=7.5$, 1.5 Hz, 1H), 5.62 (d, $J=6.6$ Hz, 1H), 5.50 (dd, $J=6.7$, 2.5 Hz, 1H), 2.47 (pd, $J=7.0$, 2.5 Hz, 1H), 1.51-1.18 (m, 4H).

1-(2-chlorophenyl)-3-cyclopropylprop-2-yn-1-ol (**7**). ^1H NMR (400 MHz, CDCl_3) δ 7.61-7.38 (m, 2H), 7.34-7.18 (m, 2H), 5.83 (dd, $J=7.0$, 2.5 Hz, 1H), 5.49 (d, $J=7.0$ Hz, 1H), 2.62 (m, $J=7.0$, 2.6 Hz, 1H), 1.49-1.21 (m, 4H).

1-(3-chlorophenyl)-3-cyclopropylprop-2-yn-1-ol (**8**). ^1H NMR (400 MHz, CDCl_3) δ 7.50-7.32 (m, 2H), 7.26 (tt, $J=7.1$, 1.5 Hz, 2H), 5.95-5.12 (m, 2H), 2.61 (pd, $J=7.0$, 2.2 Hz, 1H), 1.60-0.96 (m, 4H).

1-(4-chlorophenyl)-3-cyclopropylprop-2-yn-1-ol (**9**). ^1H NMR (400 MHz, CDCl_3) δ 7.53-6.97 (m, 4H), 5.66-5.19 (m, 2H), 2.57 (pd, $J=7.1$, 2.5 Hz, 1H), 1.37-1.28 (m, 4H).

1-(4-butoxy-3-methylphenyl)-3-cyclopropylprop-2-yn-1-ol (**10**). ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.14 (m, 2H), 6.84 (d, $J=7.4$ Hz, 1H), 5.74 (d, $J=6.6$ Hz, 1H), 5.63 (dd, $J=6.7$, 2.5 Hz, 1H), 4.02 (t, $J=7.0$ Hz, 2H), 2.58 (pd, $J=7.0$, 2.4 Hz, 1H), 2.17 (s, 3H), 1.79-1.65 (m, 2H), 1.60-1.20 (m, 6H), 0.99 (t, $J=8.0$ Hz, 3H).

3-cyclopropyl-1-(4-methoxy-3-methylphenyl)prop-2-yn-1-ol (**11**). ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.19 (m, 2H), 6.80 (d, $J=7.5$ Hz, 1H), 5.71 (d, $J=6.8$ Hz, 1H), 5.57 (dd, $J=6.7$, 2.5 Hz, 1H), 3.87 (s, 3H), 2.61 (pd, $J=7.0$, 2.6 Hz, 1H), 2.19 (s, 3H), 1.57-1.35 (m, 4H).

3-cyclopropyl-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (**12**). ^1H NMR (400 MHz, CDCl_3) δ 7.35-7.18 (m, 2H), 5.34 (s, 9H), 4.11 (pd, $J=7.1$, 2.5 Hz, 1H), 3.00-2.78 (m, 4H).

1-(5-bromo-2,4-dimethoxyphenyl)-3-cyclopropylprop-2-yn-1-ol (**13**). ^1H NMR (400 MHz, CDCl_3) δ 7.64 (s, 1H), 6.64 (s, 1H), 5.83 (dd, $J=7.0$, 2.6 Hz, 1H), 5.48 (d, $J=7.0$ Hz, 1H), 3.87 (d, $J=34.1$ Hz, 6H), 2.59 (m, $J=7.0$, 2.6 Hz, 1H), 1.66-0.87 (m, 4H).

4-(3-cyclopropyl-1-hydroxyprop-2-yn-1-yl)-5-methoxybenzene-1,2-diol (**14**). ^1H NMR (400 MHz, CDCl_3) δ 8.65 (s, 1H), 8.54 (s, 1H), 6.96 (s, 1H), 6.50 (s, 1H), 5.74 (dd, $J=7.0$, 2.5 Hz, 1H), 5.48 (d, $J=7.0$ Hz, 1H), 3.83 (s, 3H), 2.59 (pd, $J=7.0$, 2.6 Hz, 1H), 1.52-1.24 (m, 4H).

(R)-1-(anthracen-9-yl)-3-cyclopropylprop-2-yn-1-ol (**15**). ^1H NMR (400 MHz, CDCl_3) δ 8.27 (dd, $J=7.3$, 1.6 Hz, 2H), 8.15 (tt, $J=1.5$, 0.7 Hz, 1H), 7.81 (dt, $J=7.5$, 1.7 Hz, 2H), 7.30 (m, $J=25.4$, 7.5, 1.6 Hz, 4H), 5.95 (dd, $J=6.9$, 2.5 Hz, 1H), 5.47 (d, $J=6.8$ Hz, 1H), 2.39 (pd, $J=7.0$, 2.5 Hz, 1H), 1.34-0.98 (m, 4H).

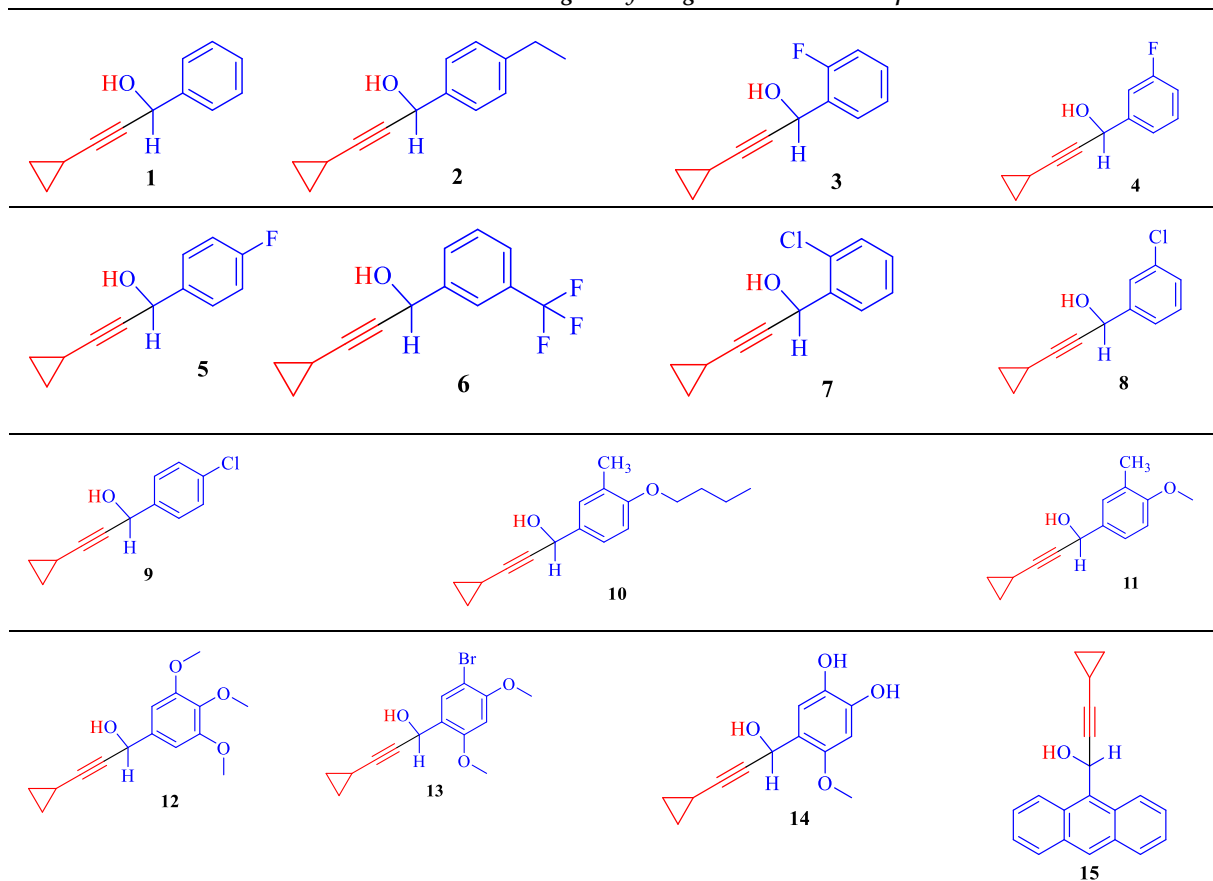


Fig. 3. Structural formula of synthesized aromatic acetylenic alcohols

3.1. Molecular docking

Molecular docking simulations were performed using the AutoDock Vina algorithm. The cryo-EM structure of the human NOX2 enzyme (PDB ID: 7U8G) was obtained from the PDB. The grid box was centered at $x=143.337$, $y=143.645$, $z=141.271$ with dimensions of $40 \times 40 \times 40$ Å. The exhaustiveness parameter was set to 64. Visualization of the docking poses was conducted using BIOVIA Discovery Studio 2020 and PyMOL.

4. CONCLUSION AND RECOMMENDATIONS

For the first time, a series of new aromatic acetylenic alcohols were synthesized via the enantioselective alkynylation of benzaldehyde and its various derivatives using cyclopropylacetylene in the presence of an $\text{EtMgCl/C}_{17}\text{H}_{29}\text{NO/TFE}$ catalytic system. The influence of the spatial structure of aldehyde molecules, the nature of their substituents, and their stability on the product yield and reaction rate were thoroughly investigated. The synthesized compounds were identified and characterized using modern physicochemical methods; their purity and structural properties were confirmed, and reaction mechanisms were proposed based on energetic and quantum-chemical calculations. These acetylenic alcohols, possessing both a hydroxyl group and a highly reactive triple bond, hold significant practical potential in fine organic synthesis, polymer chemistry, and the development of biologically active agents for pharmaceutical and agricultural applications against various bacteria and fungi.

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PHOTOCHROMISM TESTING of BaMgSiO₄:Fe WITH DIFFERENT REACTION CONDITIONS

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ARTICLE INFO	ABSTRACT
Article history: Received: 2025-12-05 Received in revised form :2025-12-16 Accepted :2026-01-26 Available online: 2026-06-26 Keywords: Photochromism, Color centers, Silicate.	In recent years, there has been an increased focus on the study of tunable inorganic photochromic(color-changing) materials. Most of the silicates have poor photochromic properties. However, by doping these particles with specific dopants, these properties can be enhanced. BaMgSiO ₄ (BMS) is a member of the silicate salts that are suitable for enhancing photochromism using various dopants. Fe as a dopant was tested under two different reaction conditions (air and N ₂ /H ₂) with photochromic BMS samples. The results revealed that the N ₂ /H ₂ atmosphere is the most effective reaction condition for synthesis.

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1. INTRODUCTION

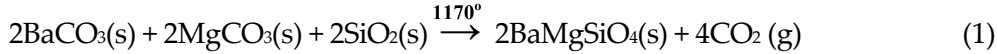
Photochromism is a reversible color change by exposure to light on the materials. A large number of photochromic materials have extensive uses globally, based on different areas such as light-responsive technologies, ranging from adaptive optical elements to biomedical applications, X-ray intensification, scintillation, dosimetry, etc. [1-3] Some research in this area focuses on the development of novel photochromic materials and the precise control of their photochromic properties to satisfy the requirements of various optoelectronic applications. For example, materials that respond to red or near-infrared light within the biological optical window (700–900 nm) have been widely used in biological applications.[4] Photochromic materials that respond rapidly to light stimuli are desirable for applications such as smart lenses. In contrast, reduced sensitivity to photoirradiation is advantageous in the field of data security, as it helps preserve stored information. Furthermore, the ability to tune the coloration rate on demand can greatly enhance the security of recorded texts, since different information may appear at different irradiation times.[5]

2. EXPERIMENTAL

Fe-ion-doped BMS powders were synthesized using a solid-state reaction approach. High-purity BaCO₃ (99.9%), MgCO₃ (99.9%), SiO₂ (99.9%), and 0.1 mol% Fe₂O₃ (99%) were used as starting materials. Additionally, 10 mol% H₃BO₃ (99.99%) was added as a flux to facilitate the reaction. [6]

The raw materials were weighed according to the stoichiometric composition of BaMgSiO₄ and thoroughly mixed in a mortar with ethanol to ensure a uniform mixture. After drying, the powder blend was transferred into an alumina reaction vessel.

Then the mixtures of these materials were transferred to an aluminum oxide reaction vessel and put into a Lenton LTF 14/25/450 oven at 1170°C for 4 hours with the heating and cooling rate of 20°C/min, under air and reducing atmosphere (12% H₂ and 88% N₂) conditions. After sintering, the reacted material was scraped and collected directly from the alumina vessel for further processing and characterization. BaMgSiO₄:X (X= First row transition metals, Eu and Dy) samples were synthesized (reaction 1) following the protocol reported by Akiyama et al. [6]



The synthesized materials were then compared using a UVP UVLS-24 EL Series (254/365 nm) and an Analytik Jena UVM-57 (302nm).

3. RESULTS AND DISCUSSION

To ensure uniformity, XRD analyses were conducted. XRD patterns were obtained using a PANalytical Aeris powder X-ray diffractometer operating at 40.0 kV and 7.5 mA, equipped with a PIXcel1D-Medipix3 detector and Cu-K $\alpha_{1,2}$ radiation ($\lambda = 1.5406 \text{ \AA}$ and $1.5444 \text{ \AA}$). The optical configuration and data acquisition conditions included a nickel β -filter, 0.04 rad Soller slits, a 1/4° divergence slit, a 13 mm fixed mask, a high beam knife, and a 9 mm anti-scatter slit. During measurements, the sample spinner operated at 1 rps, with a scan rate of 0.201 °/s and a step size of 0.0217°.

The collected XRD data were processed using HighScore together with the ICDD PDF-4+. Background correction was performed with a bending factor of 2 and a granularity value of 20 using smoothed input data. Peak detection parameters included a minimum significance of 3.00, a minimum tip width of 0.01, a maximum tip width of 1.00, and a peak base width of 2.00. Peaks were identified using the minimum second-derivative method and matched against reference patterns from the ICDD PDF-4+ database. For the synthesized materials, the most prominent phase (04-011-3561) was identified using the HighScore PANalytical software (**Figure 1**). The XRD patterns of the doped BaMgSiO₄:Fe samples synthesized in an air and reducing atmosphere indicate that the doped samples possessed the primary crystal structure independent of the reaction conditions. Well-defined peaks corresponding to the reference phase indicate successful phase formation without significant secondary phases.

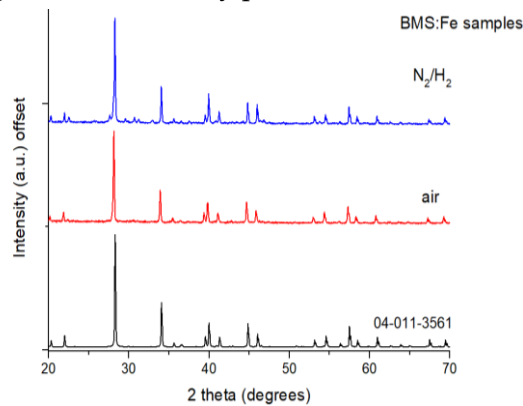


Figure 1: XRD patterns of the Fe-doped sample synthesized under air and reducing atmosphere, along with the corresponding phase identified from the software.

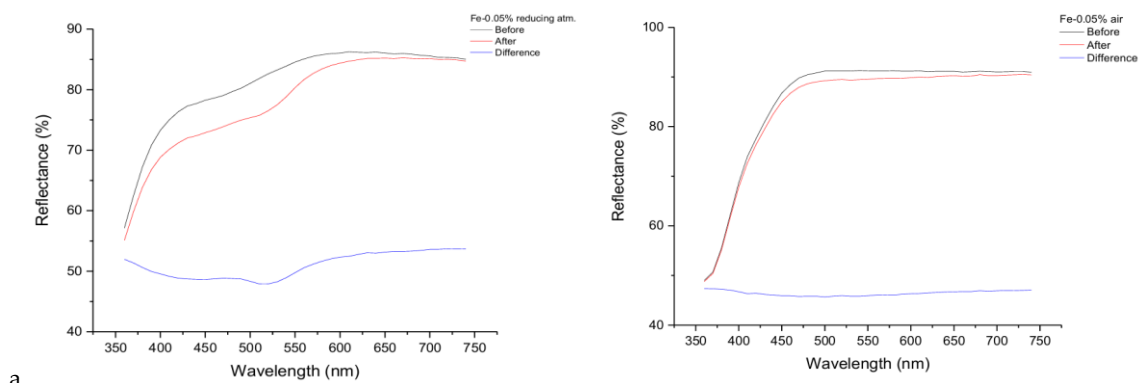
The photochromic behavior of Fe-doped BaMgSiO₄ was tested by monitoring the reflectance spectra before and after 254 nm UV irradiation for samples sintered under air and reducing atmospheres. The results (**Figure 2a**) clearly demonstrate that the synthesis atmosphere influences the nature of Fe ions and defects present in the material.

For the sample sintered under a reducing atmosphere, UV irradiation induces a pronounced decrease in reflectance across the visible region (≈ 350 –750 nm). The difference spectrum shows a broad negative feature, with the largest reflectance change occurring in the blue–green region. This behavior is characteristic of strong photochromism and suggests the formation of photo-induced color centers.[6] Under reducing conditions, Fe is more likely to exist partially as Fe²⁺, accompanied by a higher concentration of oxygen vacancies. Upon UV irradiation, electron transfer processes—such as Fe³⁺ $\rightleftharpoons$ Fe²⁺ transitions or electron trapping at oxygen vacancies—can occur, leading to increased visible-light absorption.

In contrast, the sample sintered in air exhibits a much weaker photochromic response. Although a small decrease in reflectance is still observable after UV exposure, the magnitude of the change is significantly lower and remains nearly constant across the visible range. This subdued response indicates that photo-induced charge transfer processes are less efficient in the air-sintered sample. The dominance of Fe³⁺ species and the lower concentration of oxygen vacancies under oxidizing conditions likely limit the formation of metastable trapped-electron states, thereby suppressing strong photochromism.

Comparing the two atmospheres highlights the role of defect chemistry in photochromic behavior. The stronger response of the sample treated in a reducing atmosphere is due to the combined effect of mixed-valence iron ions and oxygen vacancies. Together, they make it easier for UV radiation to move electrons and stabilize the resulting color centers. Similar mechanisms have been reported in other Fe-doped silicate and oxide-based photochromic systems, where reducing conditions favor reversible optical modulation.

Overall, these results confirm that Fe-doped BaMgSiO₄ exhibits photochromism under 254 nm UV irradiation. Sintering under a reducing atmosphere significantly enhances the photochromic contrast, making this material a promising candidate for UV-responsive optical applications such as smart pigments or optical storage, where controllable and reversible color changes are required (Figure 2).



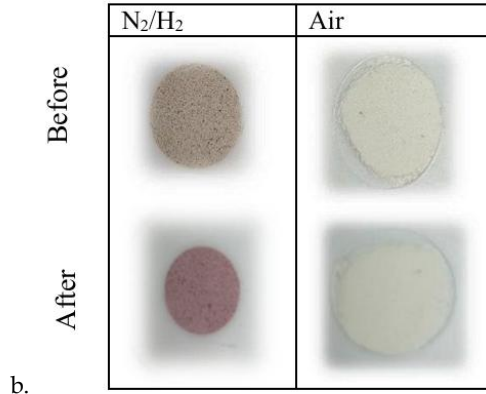


Figure 2: a. Diffuse reflectance spectra of 0.05%-Fe-doped BaMgSiO₄ sintered under reducing and air atmospheres before and after 254 nm UV irradiation; the atmosphere-dependent photochromic response.
b. Comparison of the photochromism of two materials with the same composition but with different reaction conditions, with exposure to 254 nm UV light.

4. CONCLUSION

In this study, BaMgSiO₄ (BMS) phosphors doped with Fe were synthesized via a solid-state reaction method under both air and reducing (N₂/H₂) atmospheres, and their photochromic behavior was investigated. Among the examined conditions, the reducing atmosphere proved to be the most effective for inducing photochromism in doped BMS materials.

The XRD results confirm the successful formation of the desired phase independent of the reaction conditions. The diffraction peaks match well with the reference pattern, and no significant secondary phases are observed. This indicates that the sample has good phase purity.

Detailed optical analysis of Fe-doped BaMgSiO₄ revealed a clear and reversible photochromic response upon 254 nm UV irradiation, strongly dependent on the sintering atmosphere. Samples synthesized under reducing conditions exhibited a pronounced decrease in diffuse reflectance across the visible spectrum, indicative of strong photo-induced absorption. The enhanced photochromism is attributed to mixed-valence Fe²⁺/Fe³⁺ ions and increased oxygen vacancies, facilitating efficient UV-induced electron transfer and stable color centers. In contrast, air-sintered samples show weak photochromism due to dominant Fe³⁺ species and fewer defect states.

Overall, the results demonstrate that defect engineering through controlled synthesis atmospheres plays a critical role in activating and enhancing photochromic behavior in silicate-based materials.

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SORPTION OF Ca^{2+} and Mg^{2+} ions OF SULPHOCATIONITE OBTAINED BY S MODIFICATION OF POLYVINYL CHLORIDE USING CaS_x SOLUTION

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ARTICLE INFO	ABSTRACT
Article history: Received: 2025-11-09 Received in revised form :2025-11-16 Accepted :2025-12-18 Available online: 2026-06-26	<i>In this work, $-\text{SO}_3\text{H}$ groups in the material obtained from polyvinyl chloride (PVC-SC), a new ion-exchange resin for purifying water from metal ions, were proven and their physicochemical parameters were determined. Kinetics and isotherms of sorption of Ca^{2+} and Mg^{2+} ions from artificial solutions to PVC-SC were studied. As a result, the adsorption of calcium II and magnesium II ions from aqueous solutions onto the new sulfocationite have consistent with the Langmuir isotherm. This indicated that new sulfocationite chemically adsorbed calcium II and magnesium II ions from artificial solutions.</i>
Keywords: Sulphur, sorption, cationite, calcium, magnesium, isotherm.	

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1. INTRODUCTION

Many countries are facing environmental problems due to improper disposal of industrial waste. Pollutants formed in water bodies have a harmful effect on the environment even at low concentrations. Recently, there are some methods of water purification, and ion exchange resins are widely used to remove Ca^{2+} and Mg^{2+} ions, which cause water hardness [1]. The most common reason for the purification of water from contaminants by the adsorption method is its technological simplicity, ease of process, repeated recycling of ion exchange material by recycling, and cost-effectiveness [2],[3].

Water hardness is caused by certain metals, especially calcium and magnesium ions. The sorption of Ca^{2+} and Mg^{2+} ions for water purification in the food industry from existing ion exchange resins on a weak acidic resin PC200FD was studied [4]. Adsorption of calcium to an aqueous solution of Purolite C100E synthetic ion exchange resin was studied using Langmuir and Freundlich isotherm models [5]. The authors [6] determined the structure of ion exchange resin by modifying the cellulose with amines by IR spectroscopy. The absorption rate and equilibrium of calcium and magnesium ions from artificial solutions to the made cation exchange materials were researched, with the heigh sorption value for the Langmuir isotherm model being 54.1 mg/g for calcium II and 42.6 mg/g for magniseum II. New cation exchange resin made by modification of PVC has been researched in water treatment for industrial use [7]. Some kinetic models of sorption from aqueous solutions of Ca^{2+} and Mg^{2+} ions to PVC-based

sulfonation exchange resin were studied and the amount of sorption was calculated [8]. Researchers are working on creating economically viable adsorbents for industrial wastewater treatment. One of the most important means of studying the mechanism of ion exchange of ionite is the organization of the adsorption isotherm. In recent years, the isotherm models of Langmuir, Freundlich, Temkin, Dubinin-Radushkevich have been analyzed in the study of ion sorption from solutions [9]. From the above literature, it is clear that ion exchange resins were obtained by modifying natural and synthetic polymers, and the adsorption of various metals was studied using isothermal models.

In this paper, the absorption isotherms of Ca^{2+} and Mg^{2+} ions for polyvinyl chloride-based ion exchange materials were researched.

2. Methods and materials of research

Analytical pure substances were used in the preparation, oxidation of calcium polysulfide solution and the sorption of calcium and magnesium ions to ion exchange resins for the modification of sulphur in polyvinyl chloride plastic. Analytical pure substances were used in the made, oxidation of CaS_x solution and the sorption of calcium and magnesium ions to ion exchange resins for the modification of sulfa-groups in polyvinyl chloride plastificat.

2.1. Synthesis of a cation exchange resin on the basis of PVC

2.1.1. Process of obtaining a solution of CaS_x

As a result of many experiments, the optimal conditions for obtaining a solution of CaS_x are the reaction in a flask with a mass ratio $\text{CaO}:\text{S}:\text{H}_2\text{O}$ of 1.0: 3.0: 16.8, respectively, at a temperature of 358-368 K for 70-90 minutes [10]. Additional substances such as H_2S , $\text{Ca}(\text{SH})_2$, CaS_2O_3 can be formed during the reaction. The result of the reaction is a dark red solution, which is filtered off. The mass fraction of CaS_x in the solution was found to be 28-34%. The residue can be used for re-synthesis or buried in the ground as fertilizer. A longer reaction time may lead to an increase in thiosulfate ions, but this has a positive effect on the production of cation exchange resins with sulfo groups from PVC. This is because thiosulfate ions or ion radicals, such as sulfide groups, are more likely to oxidize to sulphur groups during the oxidation process after being bonded to a PVC chain.

2.1.2. Modification of sulphur to PVC and extraction of cation exchange resins

Various experiments have been performed to modify sulphur to PVC [11]. Granular plastic PVC (grade I-40-13A) was extracted in ethyl acetate for 2 h. The goal is to increase the porosity of plastic by producing a plasticizer (dibutyl phthalate) from PVC. PVC is filtered and poured into a vessel, a boiling solution of CaS_x is poured over it, the vessel is hermetically sealed and heated at 423 K for 4 hours. In the next step, the $-\text{S}_x-$, $-\text{SH}$ groups of the sulfur-modified polymer are reacted with a concentrated solution of HNO_3 in a water bath for 3-4 hours and are oxidized to the $-\text{SO}_3\text{H}$ group.

The gained ion exchange resin was washed and the NaOH static exchange capacity (SEC) was determined, SEC value of 3.5 mg-eq/g.

2.2. Study of adsorbent properties

The physicochemical properties of synthesized sulpho-cation exchange resins were studied and element analysis and FTIR spectroscopy. The amount of elements in polyvinyl chloride-based resin was studied by Euro EA Elemental Analyzer. The spectra corresponding to the vibration of the functional groups in the obtained material were analyzed in an IRTracer-100 IR-Fourier

spectrophotometer. The study of the physicochemical parameters of the obtained cation exchanging material showed that it meets the requirements of GOST 20298-74 for use in the separation of ions available on an industrial scale. The ion exchange resin, synthesized from PVC-based plastic, has been officially registered by the Uzbekistan Institute of Standards, operating under the Agency for Technical Regulation of Uzbekistan (UZSTANDART), under the designation Ts 02072392-00:2020.

Experiments of sorption

2.3.1 Preparation and sorption conditions of metal solutions

CaCl_2 and $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$ were used to research the adsorption of Ca^{2+} and Mg^{2+} ions that cause water hardness to polyvinyl chloride-based ion exchanger materials. Aqueous solutions of calcium and magnesium ions with concentration 0.1, 0.075, 0.05 and 0.025 mol/l were made. The adsorption process was researched in solutions at temperatures difference from 293 to 313 K. The adsorption process was studied in solutions with a temperature difference from 293 to 313 K. For this, the static ion exchange capacity SEC of 3.5 mg-eq/g cationite, 2 g/l in size, was studied in 100 ml flasks at a speed of 100 rpm for different time (2-12 h.) intervals.

. Initial and equilibrium concentrations of metal solutions were determined by titration with EDTA solution. The mass of absorbed metal in ionite was calculated as follows.

$$Q_e = \frac{C_0 - C_e}{m} \quad (1)$$

where Q_e is the amount of ion absorption in mg/g, C_0 is the concentration of the ion in the initial solution in mg/l, C_e is the concentration after sorption in mg/l, V is the volume of the solution containing the ion in l; m is the dry mass of the ion exchange resin in g.

2.3.2. Isothermal models

In the analysis of equilibrium processes, one of the most important tools is the adsorption isotherm. Therefore, in this work, the adsorption mechanism was analyzed using the isotherm models of Langmuir, Freundlich, Temkin, and Dubinin-Radushkevich (D-R), which are widely used in liquid-solid systems.

3. Results and discussion

Characterization of a Cation Exchange Resin Synthesized from Polyvinyl Chloride

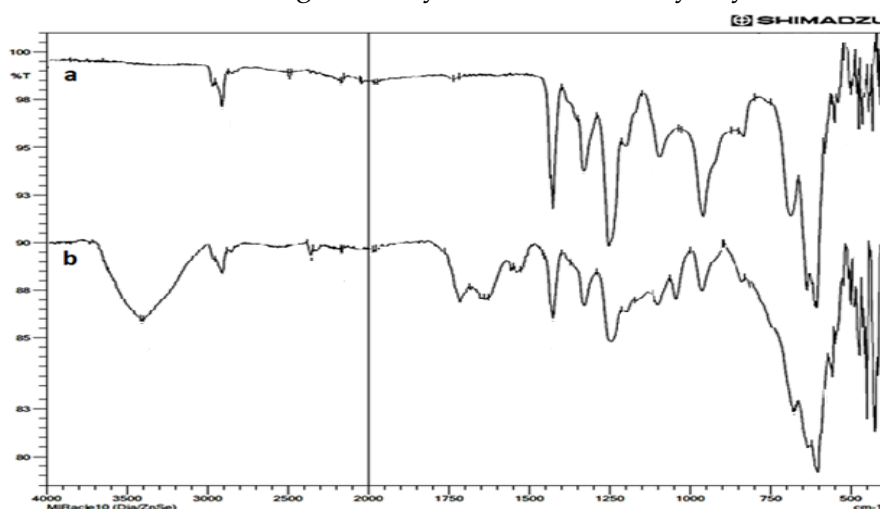


Fig 1. The functional groups in the polymer were studied by elemental analysis and IR spectroscopy of the cation exchanging composition obtained by oxidation of a polymer gained by modifying CaS_n to PVC.

3.1.1. IR spectroscopy of a cation exchange resin based on PVC

IR spectrum analysis was performed to determine the structure of the cation exchange resin oxidized with HNO_3 of the sulfurized polyvinyl chloride material modified with calcium polysulfide. 1. IR spectroscopy of PVC without polyvinyl chloride plasticizer (a) and PVC-based cation exchange resin (b).

A comparative analysis of the infrared spectroscopy data reveals the presence of sulfur groups in the cation exchange resin. In the IR spectrum shown in Figure 1-(b), distinct absorption peaks associated with the monovalent $-\text{SO}_3\text{H}$ bonds are observed at 1714 cm^{-1} and 1210 cm^{-1} , which are indicative of the functional groups present in the resin, as well as the valence oscillations of the $\text{S}=\text{O}$ bond in the $1220\text{--}1080\text{ cm}^{-1}$ area, around 3400 cm^{-1} characterizing the $-\text{OH}$ groups wide absorption areas have emerged.

This observation suggests that the sulfide, polysulfide, and hydrosulfide groups in the sulfurized polymer underwent oxidation, transforming into sulfur-containing functional groups. As shown in Figure 1 (a, b), the IR spectra exhibit distinct absorption bands at 700 cm^{-1} and 605 cm^{-1} , which are characteristic of $\text{C}-\text{Cl}$ bond stretching vibrations. This indicates that some of the chloride groups in the PVC chain are replaced by polysulfide, hydrosulfide groups. In particular, absorption peaks were detected in the regions of 2966 cm^{-1} , 2922 cm^{-1} and 2862 cm^{-1} , which are characteristic of the stretching vibrations of the $\text{C}-\text{C}$, $\text{C}-\text{H}$ and CH_2 groups in the PVC macromolecule. Additionally, deformation vibrations corresponding to the methylene groups were observed at 1420 cm^{-1} , which provides additional evidence of the structural properties of the polymer [7], [11]. This means that the polymer base chain is preserved during the stages of obtaining a sulpho-cation exchange material by modifying polyvinyl chloride.

3.1.2. Elemental analysis of the PVX-SC

The results of quantitative analysis of elements in the composition of cation exchange materials based on PVC, PVC-S, and PVC are presented in Table 1 below.

Table 1. The content of elements in the composition of PVC, PVC-S, and PVC-SC

Sample	PVX			PVX-S			PVX- SO_3H		
Element	C	H	S	C	H	S	C	H	S
Quantity(m,%)	36,4	5,2	0	29,2	4,2	14,3	22,4	4,1	10,4

It can be seen from the table above that the sulfur content of sulfur-modified PVC is 14.3%. This is because the chlorine atoms in the polymer chain may have been partially replaced by sulfur. The oxidation product of the sulfur-containing polymer to convert it to a sulpfocationite showed that it contained 10.4% sulfur, which may be related to the oxygen content of the sulpfogroups.

The presented physicochemical analyses confirm the formation of ion-exchange polymer materials with sulfate groups of sulfur-modified PVC using CaS_x and its oxidation with HNO_3 . Modern studies, in particular, using various isotherm models, were used to determine the mechanism of absorption of calcium II and magnesium II ions from artificial solutions by the new PVC-SC ion exchanger.

Adsorption Isotherms

3.2.1. Langmuir Isotherm Model

According to Langmuir's theory, adsorption occurs exclusively at specific active sites on the surface of the adsorbent. In this model, the binding energy of each adsorption site is constant,

and the adsorbate molecules form a monolayer without any interaction between the adsorbed molecules. The Langmuir equation can be expressed in the following forms (2,3):

$$Q_e = \frac{Q_{\max} \cdot (K_L \cdot C_e)}{1 + K_L \cdot C_e} \quad (2)$$

$$\frac{C_e}{Q_e} = \frac{1}{Q_{\max} \cdot K_L} + \frac{1}{Q_{\max}} \cdot C_e \quad (3)$$

Where: $Q_{\max}$ is the maximum amount of metal ions adsorbed on the ion exchanger (mg/g), K_L is the equilibrium constant in the Langmuir isotherm in equation (l/mg). To calculate the Langmuir constant, the linear equation of the Langmuir equation (3) above is used, that is, a graph is formed between C_e/Q_e and C_e and it is found from the tangent of the angle. The mechanism of interaction between the ion exchanger and metal ions in the solution can be understood by using the separation coefficient (R_L) to understand the Langmuir adsorption properties (4).

$$R_L = \frac{1}{1 + K_L C_0} \quad (4)$$

In this equation, when $0 < R_L < 1$, the sorption mechanism is considered favorable, while $R_L > 1$ indicates an unfavorable sorption mechanism, $R_L=1$ indicates a linear sorption isotherm, and $R_L=0$ indicates an irreversible adsorption [12].

Based on the results obtained in this study, a C_e/Q_e dependence graph of C_e was constructed in Figure 2 (a) to calculate the Langmuir isotherm constants. The Langmuir constants obtained using this graph is given in Table 2 below. These constants show that the maximum adsorption value ($Q_{\max}$) for Ca^{2+} and Mg^{2+} was determined to be 55.3 mg/g and 37.5 mg/g, respectively. The K_L values for Ca^{2+} and Mg^{2+} were 0.00162 and 0.00116, respectively, and the partition coefficients (R_L) were 0.134 and 0.264, respectively, indicating the favorable nature of the sorption mechanism for these metal ions on PVC-SC. The understanding that the sorption isotherms for the new PVC-SC resins for calcium II and magnesium II ions fit the Langmuir model is confirmed by the high R^2 values of 0.995 and 0.991, respectively.

3.2.2. Freundlich isotherm model

The Freundlich isotherm model used for the analysis of the adsorption process in heterogeneous systems is expressed as follows (5, 6). [13]:

$$Q_e = K_F \cdot C_e^{1/n} \quad (5)$$

$$\log Q_e = \log K_F + \frac{1}{n} \cdot \log C_e \quad (6)$$

In the equations 5 and 6, the values of the Freundlich constant K_F (mg g^{-1} (l g^{-1})ⁿ) and the sorption intensity $1/n$ ($1 < n < 10$ represent the sorption ease) are found from the intercept plotted against $\log Q_e$ and $\log C_e$. Based on the data in Figure 2 (b), the Freundlich parameters were calculated. For the sorption of calcium and magnesium ions with the Freundlich constants shown in Table 2 below, the K_F values are 8.15 and 1.14, respectively, and the sorption intensity (n) is 4.56 and 2.43, respectively, which means that the sorption process is favorable.

3.2.3. Temkin isotherm model.

This isotherm allows us to consider theories about the sorbent-sorbate interaction, binding energy. During the sorption process, the sorption of ions decreases linearly under the influence of temperature. To find the magnitudes of the Temkin isotherm, equation (7) is linearly fitted to equation (8) and plotted on a graph of $\ln C_e$ versus Q_e .

$$Q_e = \frac{RT}{b} \cdot \ln(K_T C_e) \quad (7)$$

$$Q_e = \frac{RT}{b_T} \cdot \ln K_T + \frac{RT}{b_T} \cdot \ln C_e \quad (8)$$

$$B = RT/b_T$$

$$Q_e = B \ln K_T + B \ln C_e$$

Here, B - Temkin constant J mol⁻¹, K_T – Temkin equilibrium constant l g⁻¹, R – 8,314 J mol⁻¹·K⁻¹, T-temperature K. The value of B is proportional to the adsorbate adsorption rate. K_T value represents the binding strength of adsorbate with sorbent [14]. In this work, the relationship between Q_e and lnC_e in Figure 2(b) is plotted to find the Temkin constants and calculated from the cross section of this curve. The K_T Temkin constants in Table 2 were found to be 0.0364 at sorption Ca²⁺ and 0.0137 L g⁻¹ (-73.2) at sorption Mg²⁺ and values R² (0.977 and 0.986), respectively. The sorption heat parameter (B) for Ca²⁺ and Mg²⁺ was found to be 9.7 and 8.6 J mol⁻¹, respectively.

3.2.4 Dubinin-Radushkevich (D-R) isotherm model

In heterogeneous systems, information about the adsorption energy can be obtained in accordance with the characteristic porosity of the adsorbent. The Dubinin-Radushkevich isotherm model is commonly used to represent the adsorption mechanism using a Gaussian energy distribution. The formula of the Dubinin-Radushkevich isotherm model is expressed as follows (9).

$$Q_e = Q_{D-R} \exp(-\beta \varepsilon^2) \quad (9)$$

In this equation: Q_{D-R} – Absorbed amount of adsorbate (ions) according to D-R model (mg g⁻¹), β – constant depending on adsorption energy (mol² (kJ²)⁻¹), ε – The Dubinin-Rudushkevich isotherm constant (Polanyi potential), ie the adsorption energy (kJ/mol⁻¹), is calculated as follows. (10).

$$\varepsilon = RT \ln(1 + \frac{1}{C_e}) \quad (10)$$

To calculate the Dubinin-Radushkevich isotherm constants, the equation is reduced to a linear form (11).

$$\ln Q_e = \ln Q_{D-R} - \beta \varepsilon^2 \quad (11)$$

The total free energy of adsorption E_{ads} (kJ mol⁻¹) is found by this equation (12).

$$E_{ads} = \frac{1}{\sqrt{2\beta}} \quad (12)$$

where E_{ads} explains the nature of adsorption. They state that E_{ads}<8 kJ/mol corresponds to physical adsorption, E_{ads} =8-16 kJ/mol and E_{ads} >16 kJ/mol represent the occurrence of ion exchange diffusion and ion exchange reactions, respectively [9]. In this research work, a graph dependence ε² of lnQ_e in Figure 2 (d) was formulated to calculate the D-R isotherm magnitudes for the adsorption of calcium II and magnesium II ions into PVC-SC resin. The values of the isotherm constants found using this graph are listed in Table 2. Based on the Dubinin-Radushkevich isotherm model, the maximum sorption capacity for Ca²⁺ ions of the cation exchange resin was calculated as Q_{D-R} =46.9 mg g⁻¹ and Q_{D-R} =26.3 26.3 mg g⁻¹ for Mg²⁺ ions, and the value of R² was respectively 0.927 and 0.885. The sorption free energy E_{ads} found for calcium and magnesium ions according to the D-R isotherm theory is probably 10.5 and 8.2 kJ/mol, respectively, and the adsorption of ions into PVC-SC was accompanied by an ion exchange reaction under the influence of chemical forces with a small value.

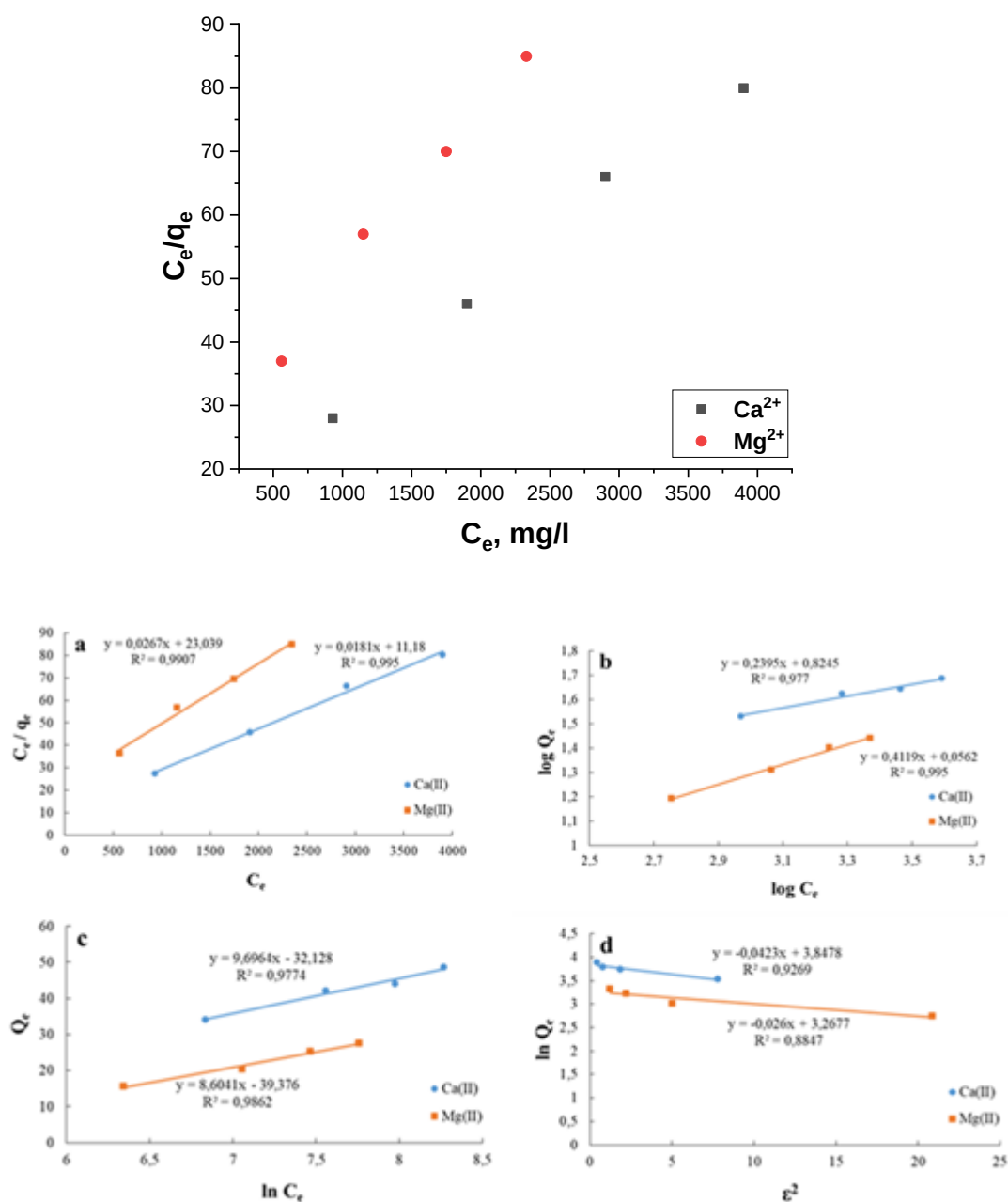


Fig 2. Expression of adsorption of Ca^{2+} and Mg^{2+} ions on PVC-based ion exchange resins in (a) Langmuir, (b) Freundlich, (c) Temkin and (d) Dubinin-Radushkevich isotherm models.

Table 2. Isothermal constants in the adsorption of metal ions on PVC-based cation exchange resins

adsorbate	Langmuir constants				Freundlich constants			Temkin constants			D-R constants		
	$Q_{\max}$	K_L	R_L	R^2	n	K_F	R^2	$-K_T$	B	R^2	Q_{D-R}	E_{ads}	R^2
Ca^{2+}	55.3	0.0016	0.134	0.995	4.56	8.15	0.977	27.7	9.7	0.977	46.9	10.1	0.927
Mg^{2+}	37.5	0.0011	0.264	0.991	2.43	1.14	0.995	73.2	8.6	0.986	26.3	8.1	0.885

4. Conclusion

- CaS_x solution was initially used to modify PVC with sulphur to produce an ion exchange resin containing sulpha groups. In the next step, a nitric acid solution was used to oxidize the hydrosulphides groups in the resulting macromolecule to sulpha groups. According to the results of elemental analysis, the cation exchange resin obtained contained 14.3% sulphur and the presence of sulpha groups was proven by IR spectroscopy.
- The sorption isotherms for Ca^{2+} and Mg^{2+} ions were successfully developed on the PVC-based cation exchange resin. As a result of studying Langmuir isotherm, Freundlich isotherm, Temkin isotherm and Dubinin-Radushkevich isotherm model, $R^2 > 0.88$ was achieved and it was shown that this sorption process is suitable for these models. According to Langmuir's monomolecular theory, the high sorption capacity Q_{max} is equal to 55.3 mg g^{-1} (Ca^{2+}) and 37.5 mg g^{-1} (Mg^{2+}) and the R_L worth (between of 0-1 at all concentrations of Ca^{2+} and Mg^{2+}) and the value n of Freundlich constant of 4.56 (Ca^{2+}) and 2.43 (Mg^{2+}) confirms that the sorption process is convenient. In the Temkin isotherm, the adsorption energy was determined to be $0.268 \text{ kJ}\cdot\text{mol}^{-1}$ and $0.303 \text{ kJ}\cdot\text{mol}^{-1}$ for Ca^{2+} and Mg^{2+} ions, respectively. The adsorption process, as modeled by the Dubinin-Radushkevich equation, suggests that the free energy (E_{ads}) for calcium and magnesium ions indicates their chemical sorption, with values of $10.5 \text{ kJ}\cdot\text{mol}^{-1}$ and $8.2 \text{ kJ}\cdot\text{mol}^{-1}$, respectively.
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REVIEW ARTICLE: APPLICATION OF GRAPHENE OXIDE NANOMATERIALS FOR ENHANCED OIL RECOVERY AND CRUDE OIL TREATMENT

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ARTICLE INFO	ABSTRACT
Article history: Received: 2025-10-25 Received in revised form :2025-11-19 Accepted :2025-12-26 Available online: 2026-06-26 Keywords: enhanced oil recovery; nanofluids; graphene oxide; interfacial phenomena; wettability alteration;	This paper presents a critical and comprehensive review of advanced approaches to enhanced oil recovery (EOR) and crude oil treatment through the use of chemical reagents and engineered fluid systems. Particular attention is given to the emerging role of graphene oxide (GO) nanomaterials in improving the efficiency of displacement processes under challenging reservoir conditions. The study systematically analyzes the fundamental mechanisms governing oil recovery, including interfacial phenomena, wettability alteration, and mobility control. Unlike conventional descriptions, this review distinguishes between true interfacial tension (IFT) reduction and particle-induced interfacial stabilization, highlighting the specific role of GO in forming Pickering-type emulsions and modifying interfacial rheology. The behavior of GO-based nanofluids is critically evaluated with respect to salinity, temperature, and rock-fluid interactions. Limitations related to nanoparticle aggregation, adsorption on porous media, and scale-up challenges are explicitly addressed. Quantitative ranges of performance enhancement reported in laboratory studies are discussed alongside their limitations in field applications. The paper introduces a refined conceptual framework for hybrid EOR systems combining surfactants, polymers, and nanomaterials, emphasizing synergistic and antagonistic interactions. Future research directions are proposed, focusing on surface functionalization, transport control, and environmentally responsible design of nanofluids.

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1. INTRODUCTION

The progressive depletion of conventional hydrocarbon reserves and the increasing reliance on mature and complex reservoirs necessitate the development of advanced recovery technologies. Primary and secondary recovery methods typically extract only 20–40% of the original oil in place (OOIP), leaving a substantial fraction trapped due to capillary forces, unfavorable mobility ratios, and reservoir heterogeneity [1].

Chemical enhanced oil recovery (EOR) methods—including surfactant flooding, polymer flooding, and alkaline-surfactant-polymer (ASP) systems—have been widely applied to address these limitations. The effectiveness of such systems strongly depends on interfacial activity, adsorption behavior, and micellization processes of surfactants, as demonstrated in previous studies [3]. The molecular structure of surfactants, including head-group composition and hydrophobic chain length, plays a critical role in controlling interfacial properties and adsorption

efficiency [4]. These methods target key physicochemical parameters such as interfacial tension (IFT), wettability, and fluid mobility [2]. However, their effectiveness is often constrained by harsh reservoir conditions, including high salinity, elevated temperatures, and complex mineralogy, which lead to chemical degradation, precipitation, and adsorption losses [5,6].

In recent years, nanotechnology has emerged as a promising approach to overcome these limitations. Among various nanomaterials, graphene oxide (GO) has attracted significant attention due to its high specific surface area, tunable surface chemistry, and amphiphilic character [7,8]. These properties enable GO to interact with both aqueous and hydrocarbon phases, as well as with solid surfaces [9].

However, despite numerous studies reporting improved oil recovery using GO, the underlying mechanisms are often oversimplified or misinterpreted. In particular, the distinction between true IFT reduction and interfacial stabilization by solid particles is frequently overlooked. Moreover, the stability and transport behavior of GO under realistic reservoir conditions remain insufficiently understood [10,11].

This review aims to provide a critical reassessment of the role of graphene oxide in EOR processes, emphasizing mechanistic clarity, experimental limitations, and pathways toward field-scale implementation [12].

2. FUNDAMENTAL MECHANISMS OF CHEMICAL EOR

Oil displacement efficiency in porous media is controlled by the balance between viscous and capillary forces acting within the pore space. This balance determines the ability of the injected fluid to mobilize and displace trapped oil. When capillary forces dominate, a significant portion of oil remains immobilized within pore throats due to interfacial tension and rock–fluid interactions. In contrast, when viscous forces are sufficiently strong, the displacing fluid can overcome capillary trapping and transport oil toward production wells [13].

An increase in oil recovery efficiency therefore requires a shift in this balance. This can be achieved through two fundamentally different approaches. The first involves reducing interfacial tension between oil and water, typically by using surfactants, which weakens capillary forces and facilitates the detachment of oil from rock surfaces. The second approach focuses on increasing the viscosity of the displacing fluid, commonly through polymer addition, which enhances the stability of the displacement front and improves sweep efficiency. These mechanisms act through distinct physical pathways and should not be considered interchangeable [14].

Another key parameter governing displacement efficiency is the mobility ratio between the displacing and displaced fluids. This parameter reflects the relative ease with which each fluid moves through the porous medium. A favorable mobility ratio, in which the injected fluid is less mobile than the oil, promotes a stable displacement front and reduces the occurrence of viscous fingering, thereby improving macroscopic sweep efficiency [15].

Wettability is an additional critical factor influencing oil recovery. It determines the preferential affinity of the rock surface toward either water or oil and directly affects fluid distribution and capillary trapping within the pore network. In many cases, shifting the system toward more water-wet conditions enhances oil recovery by promoting the release and transport of oil from the rock surface. However, the extent and direction of this effect depend strongly on reservoir-specific factors, including mineral composition, crude oil properties, and brine chemistry [16].

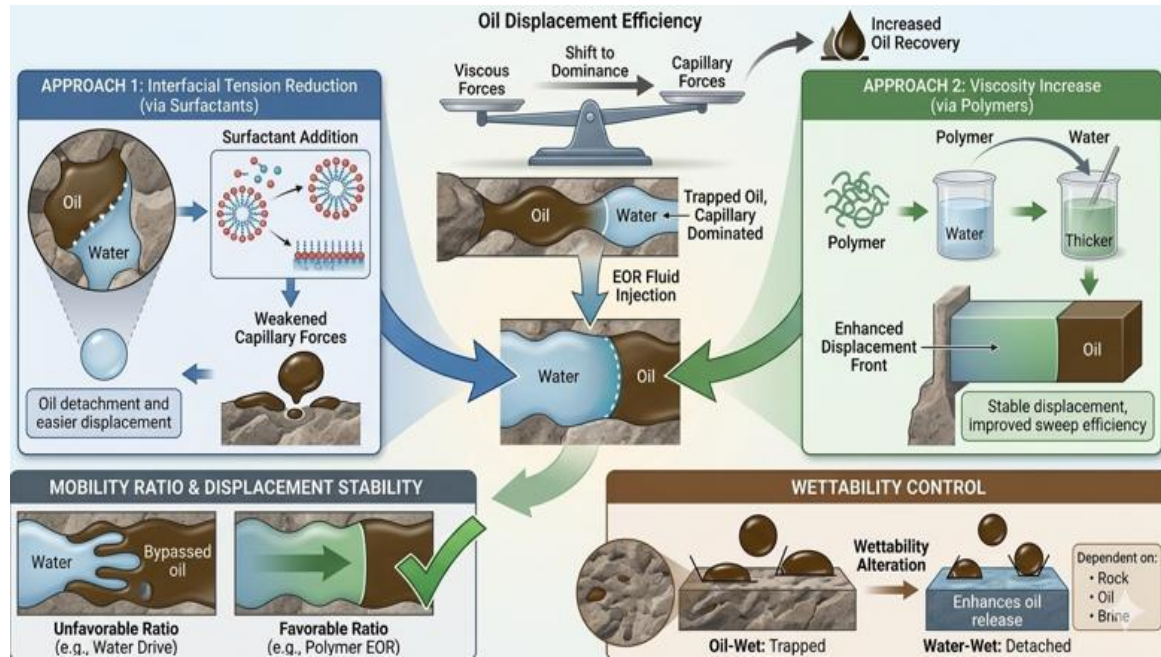


Fig 1. Fundamental Mechanisms of Chemical EOR

3. GRAPHENE OXIDE: PROPERTIES AND LIMITATIONS

Graphene oxide consists of single-layer carbon sheets functionalized with oxygen-containing groups such as hydroxyl, epoxy, and carboxyl moieties. These functional groups impart hydrophilicity and enable dispersion in aqueous media, while the graphitic domains retain affinity toward hydrophobic phases. As a result, graphene oxide exhibits amphiphilic behavior, allowing it to interact with oil–water interfaces and participate in multiphase flow processes.

Despite these advantageous properties, several important limitations must be carefully considered when evaluating its applicability in enhanced oil recovery [17].

One of the primary challenges is related to dispersion stability under reservoir conditions. Graphene oxide is prone to aggregation at high ionic strength, particularly in the presence of divalent cations such as calcium and magnesium, which can screen electrostatic repulsion and promote particle clustering. In addition, elevated temperatures may induce partial thermal reduction of graphene oxide, leading to changes in its surface chemistry and a decrease in its hydrophilicity. As a consequence, the stability of graphene oxide dispersions is strongly dependent on parameters such as salinity, pH, and the degree of surface functionalization, and often requires additional stabilization strategies for practical applications [18].

Another critical factor is the interaction of graphene oxide with reservoir rocks. Experimental studies indicate that graphene oxide can exhibit significant adsorption on mineral surfaces, particularly in carbonate formations and clay-rich sandstones. This behavior is driven by a combination of electrostatic interactions and π – π bonding with organic and mineral components. Such adsorption leads to a reduction in the concentration of active nanomaterial in the flowing phase and limits its transport through porous media, thereby decreasing its effectiveness in deeper reservoir regions [19].

In addition to physicochemical limitations, environmental considerations remain an area of uncertainty. The potential toxicity of graphene oxide and its long-term behavior in subsurface environments are not yet fully understood. Questions remain regarding its persistence, possible

accumulation, and interactions with ecological systems, which necessitate further investigation before large-scale field deployment can be considered environmentally sustainable [20].

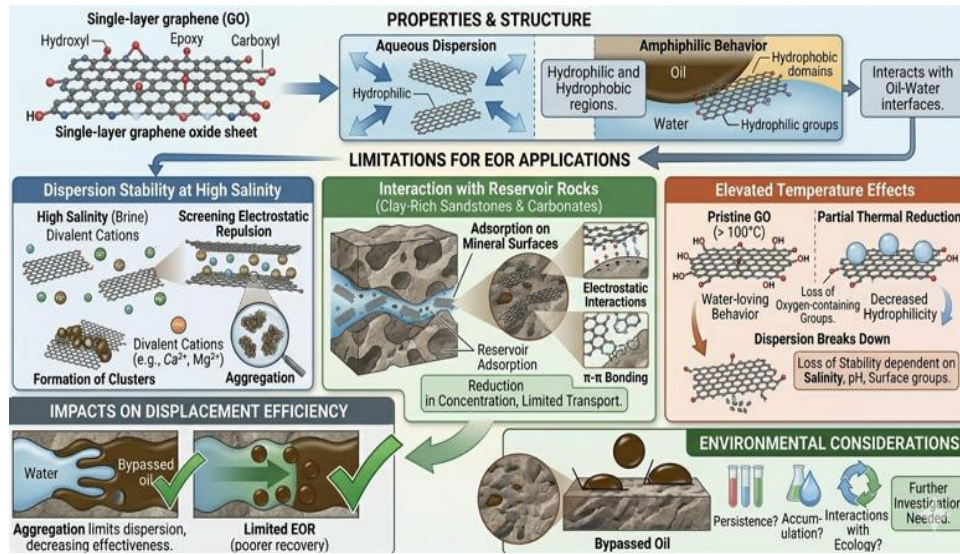


Fig 2. Graphene Oxide: Properties and Limitations

4. MECHANISMS OF GRAPHENE OXIDE IN OIL RECOVERY

4.1 Interfacial Effects

Unlike conventional surfactants, graphene oxide does not inherently act as a strong interfacial tension reducer. Its primary contribution at oil–water interfaces is related to adsorption and the stabilization of dispersed phases. Specifically, graphene oxide sheets can accumulate at fluid interfaces, forming thin, partially rigid layers that act as physical barriers to coalescence. This behavior often leads to the formation of Pickering emulsions, where solid nanoparticles stabilize droplets rather than altering the molecular-level interfacial tension. In addition, the presence of graphene oxide at the interface can modify interfacial rheology, increasing resistance to droplet deformation and breakup [19,20]. Collectively, these effects enhance emulsion stability and can contribute to improved flow diversion within porous media, promoting more uniform displacement of oil.

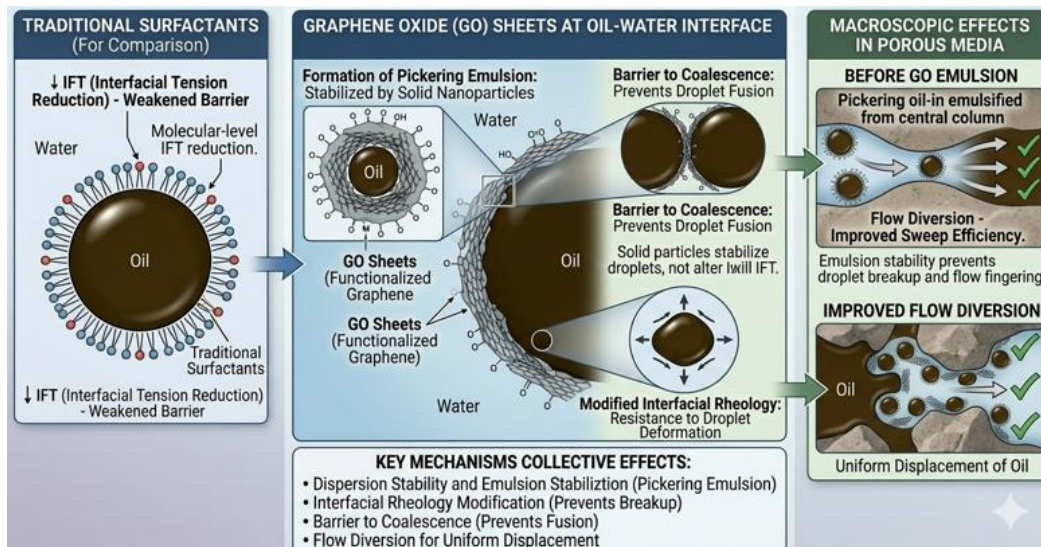


Fig 3. Interfacial Effects

4.2 Wettability Alteration

Graphene oxide has also been reported to influence rock wettability, potentially shifting surfaces toward a more water-wet state by modifying the surface energy of mineral interfaces. However, this effect is highly dependent on reservoir-specific factors, including mineralogy, crude oil composition, and brine chemistry. For example, carbonates and clay-rich formations may interact differently with graphene oxide due to variations in surface charge and organic content. As a result, wettability alteration is not universally observed and should be considered a conditional mechanism that may enhance recovery only under certain reservoir conditions [21,22].



Fig 4. Wettability Alteration

4.3 Flow Modification

Beyond interfacial interactions, graphene oxide particles can influence fluid flow patterns within the reservoir. By selectively accumulating in high-permeability channels, nanoparticles can partially block preferential flow paths, redistributing injected fluids into previously unswept or lower-permeability zones. This mechanism improves macroscopic sweep efficiency, reducing bypassed oil zones. However, such flow modification can also introduce operational challenges, including injectivity reduction or localized formation damage if particle concentration or aggregation is not carefully controlled. Optimizing nanoparticle size, surface functionalization, and injection strategy is therefore critical to harnessing the benefits of graphene oxide while avoiding adverse effects [12,16].

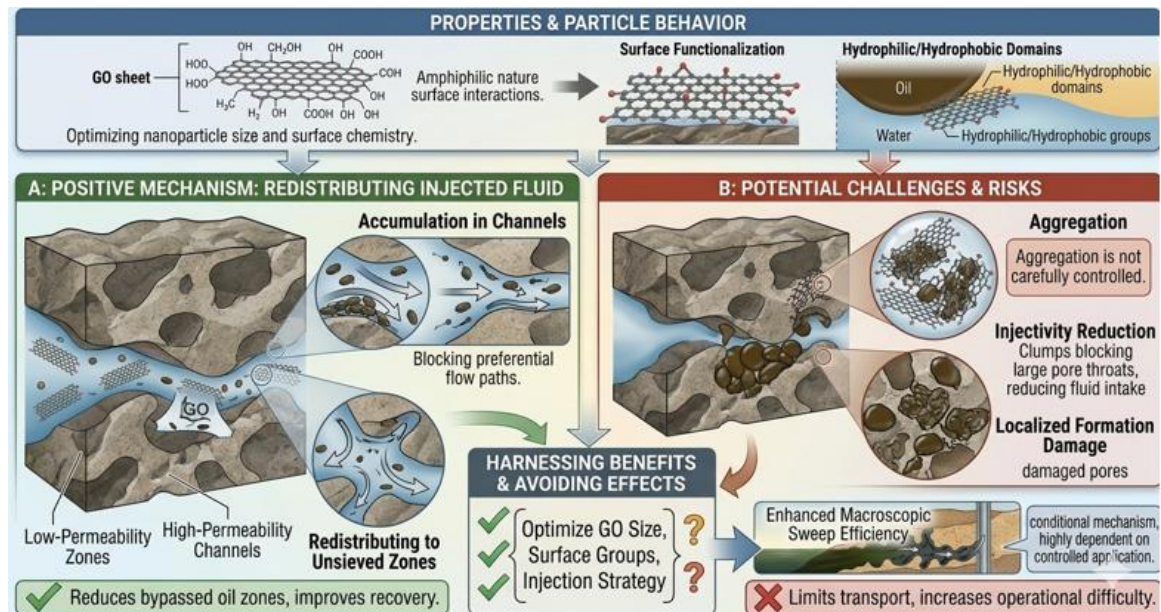


Fig 5. Flow Modification

5. HYBRID SYSTEMS INVOLVING GRAPHENE OXIDE

Graphene oxide is frequently integrated with conventional chemical agents, such as polymers and surfactants, to form hybrid systems that leverage complementary mechanisms for enhanced oil recovery. In polymer–graphene oxide formulations, the interaction between graphene oxide sheets and polymer chains can lead to a three-dimensional network structure, which increases solution viscosity and enhances viscoelasticity. This improved rheological behavior can enhance resistance to shear degradation during injection and propagation through porous media [17]. Nevertheless, these systems are sensitive to aggregation phenomena, which can compromise stability, and their effectiveness is strongly dependent on polymer concentration, molecular weight, and the surface chemistry of graphene oxide [18, 19].

Surfactant–graphene oxide combinations exhibit synergistic effects that arise from the complementary roles of each component. While surfactants actively reduce interfacial tension between oil and water, graphene oxide contributes primarily through interfacial adsorption and stabilization, improving the persistence and mechanical integrity of emulsions [20,21]. By combining these mechanisms, hybrid systems can achieve more uniform displacement fronts and potentially mobilize residual oil more effectively than single-component formulations.

Despite promising laboratory results, several performance limitations remain. Core flooding experiments often report incremental oil recovery of up to 20–30% of the residual oil; however, these outcomes are highly system-specific and depend on the particular reservoir analog, fluid properties, and experimental conditions. In practice, field-scale performance is generally lower due to the intrinsic heterogeneity of reservoirs, scale-up challenges, and operational constraints such as injectivity, pressure management, and nanoparticle retention. Consequently, while hybrid graphene oxide systems represent a promising avenue for enhancing recovery efficiency, their translation from laboratory to field requires careful optimization, reservoir-specific design, and rigorous evaluation of economic and operational feasibility [23].

6. TOWARD FIELD IMPLEMENTATION: CHALLENGES AND OPPORTUNITIES

Despite the promising laboratory-scale performance of graphene oxide-based systems, several key barriers hinder their widespread industrial application. One of the primary challenges is related to transport and retention within the reservoir. Graphene oxide is prone to adsorption onto mineral surfaces and can be physically filtered in pore constrictions, which significantly reduces penetration depth and limits the effectiveness of deep reservoir treatments. Ensuring uniform distribution throughout heterogeneous formations remains a major engineering challenge.

Stability control represents another critical limitation. The physicochemical behavior of graphene oxide is highly sensitive to salinity, divalent cations, pH, and temperature. Effective deployment often requires surface functionalization or chemical modification to maintain dispersion stability and compatibility with complex reservoir brines. Without such optimization, aggregation or sedimentation can occur, reducing the activity of the nanofluid and impairing oil recovery efficiency.

Economic viability is an additional concern. The large-scale synthesis and production of graphene oxide with consistent quality and functionalization remain costly, and the predictability of field-scale performance introduces further uncertainty. While laboratory experiments demonstrate significant potential, translating these findings into economically feasible operations requires careful assessment of cost–benefit trade-offs and scalability.

To address these challenges, emerging research directions focus on both fundamental understanding and engineering innovation. Mechanism-based nanofluid design is gaining attention, emphasizing the separation of functional roles, such as interfacial tension reduction versus interface stabilization, to optimize performance. Surface-engineered graphene oxide with controlled charge and hydrophilicity is being explored to improve stability and transport within reservoir formations. The development of smart hybrid systems, including stimuli-responsive nanofluids, offers the potential to dynamically adapt to changing reservoir conditions. Finally, multiscale modeling that links pore-scale physics to field-scale behavior is increasingly recognized as a critical tool for predicting and optimizing the performance of graphene oxide-based enhanced oil recovery strategies.

Collectively, these research avenues not only address current limitations but also define a roadmap for next-generation chemical EOR technologies. By integrating mechanistic understanding, materials engineering, and predictive modeling, future graphene oxide formulations have the potential to overcome existing barriers and enable more efficient, cost-effective, and sustainable hydrocarbon recovery in complex reservoirs.

7. CONCLUSION

Graphene oxide represents a promising but complex additive for enhanced oil recovery. Its primary contribution lies not in conventional surfactant-like behavior, but in interfacial stabilization, wettability modification under specific conditions, and interaction with multiphase flow in porous media.

However, its performance is highly dependent on reservoir conditions, and significant challenges remain regarding stability, adsorption, and scalability. While laboratory studies demonstrate encouraging results, translation to field-scale applications requires further mechanistic understanding and engineering optimization.

Future progress in this field will depend on integrating nanomaterial science with reservoir engineering, supported by quantitative modeling and realistic experimental validation.

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FACTORS AFFECTING THE DIRECTION AND YIELD OF ALKYLATION REACTIONS OF α -PHOSPHORYLCARBONYL COMPOUNDS WITH HALOCARBONYL DERIVATIVES

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ARTICLE INFO	ABSTRACT
Article history: Received: 2025-09-08 Received in revised form: 2025-09-20 Accepted: 2025-11-21 Available online: 2026-06-26 Keywords: alkylation, carbonyl compounds, carbene, phosphonoacetic aldehyde acetal	<i>The article presents the results of studies on the alkylation of α-phosphorylated carbonyl compounds with halide carbonyl derivatives. The influence of the nature of the reagents and solvents is established. The results of an in-depth study of the alkylation reaction of the more reactive phosphonoacetic aldehyde and the less reactive phosphonoacetates are presented. It is noted that the reaction direction depends on the reaction conditions, and the low yield of the target products is due to the self-condensation of the reagents under the reaction conditions. It was revealed that alkylation of the above reactions in the presence of Na in toluene forms only C-alkylation products. Differences in the direction of the alkylation reaction depending on the choice of reaction conditions are also noted. It is noted that hydrolysis of diethyl acetal with 3% HCl leads to the formation of dialdehyde, which is converted into the corresponding furan under the reaction conditions. It was also established that diacetal at temperatures above 200°C undergoes alcohol elimination, which occurs selectively from the acetal fragment located closer to phosphorus in the compound.</i>

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1. INTRODUCTION

Among the numerous classes of organic compounds, carbonyl compounds occupy a special place. They are widespread both in nature and in industry and play an important role in the biochemical processes of living organisms.

The chemical properties of carbonyl compounds are largely determined by the structure of the carbonyl group, which determines their high reactivity and ability to enter into a variety of chemical reactions [1-9].

The presence of a phosphorus fragment gives specific features to the chemical behavior and physicochemical properties of carbonyl compounds.

In [10-13], it was shown that phosphorylated compounds with an active methylene group undergo alkylation reactions characteristic of 1,3-dicarbonyl compounds. However, the replacement of the carbonyl group with a phosphorylated functional unit leads to the appearance of various features in the chemical properties of these compounds [14-17].

Systematic studies of the reaction of α -phosphorylated carbonyl compounds with halogenated alkanes have shown that the alkylation reaction involves both the active methylene group and the oxygen atoms of the carbonyl and phosphorylated groups, forming oxygen-containing heterocycles with a phosphorus atom in the ring or side chain [18-20].

That's why it is of prime interest to study the alkylation reaction of phosphoryl carbonyl compounds with halogenated carbonyl derivatives.

2. EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker AV-300 spectrometer [operating frequencies of 300 (H) and 75 (C) MHz] using TMS as the internal standard. Elemental analysis was performed on a Carlo Erba 1106 instrument. The purity of the obtained compounds was monitored by TLC on Silufol UV-254 plates. Melting points were determined using an SMP 30 instrument.

General method for the alkylation of α -phosphorylcarbonyl compounds with halogenated compounds. A halogenated compound (20 mmol) was added dropwise with vigorous stirring to a mixture of 20 mmol of phosphorylated carbonyl compounds and 20 mmol of K_2CO_3 in 50 ml of DMSO or DMF. The mixture was stirred for 2 h at room temperature, followed by heating at 60-70°C for an additional 2 h. The reaction mixture was cooled with ice water (5-10 °C), treated with water, and extracted with ether. The extract was dried over Na_2SO_4 , the ether layer was removed by distillation, and the residue was distilled under vacuum.

3-oxo-5-diethoxyphosphoryl-2,4-tetrahydroxynan (1). Dark yellow precipitate **1** was obtained from 4 g of phosphonoacetaldehyde and 3.2 g of 1,3-dichloroacetone. Yield 3.2 g (29%), mp 123-125 °C. ^1H NMR spectrum (CDCl_3), δ ppm: 1.1 t (6H, 2CH_3 , $^3J_{\text{HH}}$ 7.2 Hz), 2.3 k (2H, $=\text{C}-\text{CH}_2$), 3.9-4.0 m (4H, 2OCH_2), 4.3 s (2H, OCH_2), 7.20 s (1H, $=\text{CH}$). ^{13}C NMR spectrum (CDCl_3): δ ppm 16.24, 19.63, 22.54, 29.54, 46.49, 61.65, 63.64, 98.47, 163.08, 196.79. Found, %: C 54.11; H 7.23; P 16.32.

$\text{C}_9\text{H}_{16}\text{O}_3\text{P}$ Calculated, %: C 52.98; H 7.58; P 15.43.

Tetraethyl (2-oxoethane-1,1-diyl)bis(phosphonate) (2). 4 g of diethylphosphonoacetic aldehyde, 9 g of K_2CO_3 in 50 ml of DMF were heated for 12 h at 80 °C. The reaction mixture was cooled, treated with water and extracted with ether. The extract was dried with Na_2SO_4 , the ether portion was distilled off, the residue was distilled under vacuum, after which product **2** was obtained. Yield 3.4 g (61%), bp 146-148 °C (2 mm Hg), n_D^{20} 1.4310. ^1H NMR spectrum (CDCl_3) δ ppm: 1.08-1.22 m (12H, 4CH_3), 3.05 k (1H, CH), 3.75 – 4.0 (8H, 4CH_2), broadened s (1H, CH). Found, %: C 37.67; H 7.09; R 19.87. $\text{C}_{10}\text{H}_{22}\text{O}_7\text{P}_2$ Calculated, %: C 37.97; H 6.69; R 19.62.

Diethyl vinyl phosphate (4). Under similar conditions in the presence of DMSO, **4** is formed. Yield 0.8 g (14%), bp. 132-135 °C. ^1H NMR spectrum (CDCl_3) δ ppm: 1.25 m (6H, 2CH_3), 4.46 m (4H, 2OCH_2), 5.91 m (2H, $2\text{CH}=\text{CH}_2$), 6.15 m (1H, CH). Found, %: C 44.23; H 7.06; R 18.67. $\text{C}_6\text{H}_{13}\text{O}_3\text{P}$ Calculated, %: C 43.90; H 7.92; R 18.90.

The white powder that precipitated from the solution is dimethyl sulfone. Yield 2.8 g (66%), m.p. 109-111°C.

β -(2,2-Diethoxy-1-ethyloxy)vinylphosphonate (5). 6.5 g of bromoacetaldehyde diethyl acetal was added with stirring to a mixture of 8 g of phosphonoacetaldehyde, 6 g of K_2CO_3 in 50 ml of DMF at room temperature. The mixture was stirred at 60 °C for 5 hours, cooled, treated with water and extracted with ether. The extract was dried over Na_2SO_4 . After distilling off the ether

portion, a liquid mass with crystals was formed. The liquid portion was separated and distilled under vacuum, obtaining **5**. Yield 2.2 g (21%), bp 123-125 °C (2 mmHg), n_D^{20} 1.4480. ^1H NMR spectrum (CDCl_3) δ ppm: 0.9 t (6H, 2CH₃), 1.1-1.2 t (6H, 2CH₃), 3.6 d (2H, OCH₂), 3.7-4.1 m (8H, 4CH₂O), 4.8 t (1H, CH), 6.4 q (1H, CH), 7.2 q (1H, CH). Found, %: C 49.11; H 7.65; P 9.05; C₁₂H₂₅O₆P Calculated, %: C 48.64; H 8.44; P 10.47.

Diethyl(4,4-diethoxybutan-2-yl)phosphonate(6). Crystalline part – product **6**. Yield 0.8 g (10%), m.p. 43-44 °C. ^1H NMR (CDCl_3) δ ppm: 1.1-1.3 m (12H, 4CH₃), 1.35 m (2H, CH₂), 3.5 m (1H, CH), 4.1-4.2 m (8H, 4OCH₂), 4.85 t (1H, CH<), 9.2 hp. (1H, CH=O).₃

General method for the alkylation of α -phosphorus- α -carbonyl compounds. 2-phosphonoacetate in 50 ml of toluene was stirred at 50-60°C for 3-4 hours until complete dissolution. After complete dissolution of the sodium, bromoacetal (100 mmol) was added, the mixture was stirred for 2 hours, the precipitated salt was filtered off, the toluene was removed, and the residue was distilled under vacuum.

Diethyl (1,1,4,4-tetraethoxybutan-2-yl)phosphonate (7). From 3.5 g of diethyl-

phosphonoacetaldehyde diacetal and 3.0 g of bromoacetaldehyde diethyl acetal, **7** was obtained according to the above procedure. Yield 2.6 g (48%), bp 150-151 °C (2 mmHg). NMR ^1H ($\text{DMSO}-d_6$) δ ppm: 0.9-1.1 m (18H, 6CH₃), 1.61 (2H, CH₂), 3.2 m (1H, CH), 3.7-4.08 m (12H, 6CH₂), 4.86 m (2H, 2CH). Found, %: C 52.34; H 9.12; P 9.23 C₁₆H₃₅O₇P Calculated, %: C 51.89; H 9.45; P 8.37

3-diethoxyphosphoryl furan (9). Product **9** was obtained in high yield by hydrolysis of acetals 6,7,8 with 3% HCl at room temperature. Yield 92%, bp 120 °C (1 mmHg), d_4^{20} 1.1082. ^1H NMR spectrum (CDCl_3) δ ppm: 1.20 m (6H, 2CH₃), 4.25 m (4H, 2CH₂=O), 6.34 q (1H, CH), 7.15 d (2H, 2CHO). Found, %: C 47.78; H 6.98; P 14.65. C₈H₁₃O₄P Calculated, %: C 47.05; H 6.37; P 15.19.

Reaction of triethylphosphonoacetate with ethyl α -bromopropionate. To a mixture of 5 g of triethylphosphonoacetate, 10 g of potash in 50 ml DMSO 4 g of ethyl 2-bromopropionate was added with stirring, followed by heating to 70-80 °C for 6 hours. The mixture was cooled, treated with water and extracted with ether, dried over Na₂ SO₄. The ether part was distilled off. After distilling off the ether, the crystalline precipitate of diethyl 2,2-(1,1,3-triethoxy-1,3-dioxo-1,3-diphosphoxane-1,3-diyl)diacetate (**10**) was filtered off. Yield 4.1 g (53%), mp 94-95 °C. ^1H NMR spectrum (CDCl_3) δ ppm: 1.15 t (6H, 2CH₃), 1.20 t (6H, 2CH₃), 2.75 d (4H, 2CH₂), 3.95-4.1 m (4H, 2CH₂), 4.2 m (4H, 2CH₂). ^{13}C NMR spectrum (CDCl_3) δ ppm: 14.63, 16.85, 34.39; 36.34, 60.80, 61.42, 167.81. Found, %: C 40.34; H 5.78; P 15.44 C₁₄H₂₉O₁₀P₂ Calculated, %: C 40.10; H 6.92; R 14.79. The filtrate was distilled: the first fraction was diethyl ester of dimethylmaleic acid (**11**), the second fraction was ethyl ester of dimethylfumaric acid (**12**) described in [20].

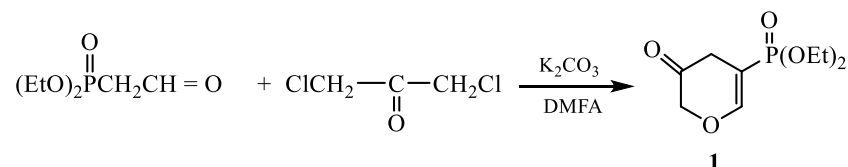
Ethyl 2-diethoxyphosphoryl)-4,4-diethoxybutanoate (13). 4 g of triethylphosphonate and 0.5 g of chopped sodium in 30 ml of toluene were stirred at 60 °C until the metal was completely dissolved, then the mixture was cooled to 10-15 °C and 5 g of bromoacetaldehyde diethyl acetal were added. The mixture was heated to 50-60 °C and stirred for 2-3 hours. It was cooled and filtered; the solvent was distilled off, and the residue was distilled under vacuum. The yield of product **13** was 3.4 g (46%), bp 126-127 °C (2 mmHg), n_D^{20} 1.4390. ^1H NMR spectrum ($\text{DMSO}-d_6$) δ ppm: 0.9-1.0 m (9H, 3CH₃), 1.1-1.2 m (6H, 2CH₃), 1.52 m (2H, CH₂), 3.3 m (1H, CH), 3.7-4.1 m (10H, 5CH₂), 4.8 t (1H, CH). Found, %: C 48.76; H 7.65; P 9.41 C₁₃H₂₉O₇P Calculated, %: C 49.41; H 8.50; R 9.11.

Diethyl 2-(diethoxyphosphoryl)-3-methylsuccinate (14). Similarly, **14** was obtained from 4 g of triethylphosphonate and 3 g of ethyl bromopropionate. Yield 5.3 g (48%), bp. 113-115 °C (2 mm

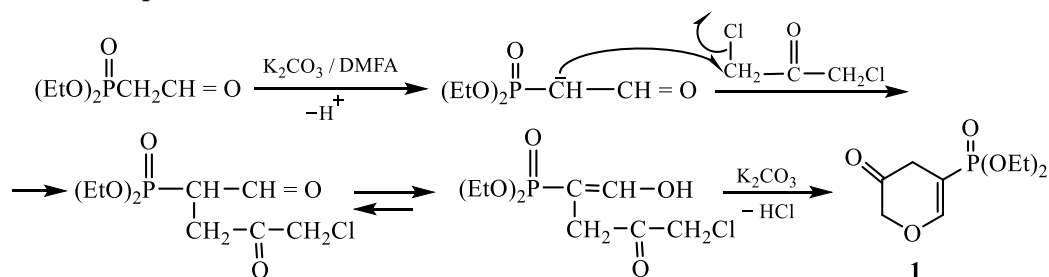
Hg), nm^{20} 1.4490. ^1H NMR spectrum (DMSO- d_6) δ ppm: 0.8 d (3H, CH_3), 1.0 t (3H, CH_3), 1.1-1.2 m (6H, 2CH_3), 2.6 m (1H, CH), 3.1 k (1H, CH), 3.7 m (4H, 2CH_2), 3.9-4.1 m (4H, 2CH_3). Found, %: C 48.67; H 7.96; P 9.96 $\text{C}_{13}\text{H}_{25}\text{O}_7\text{P}$ Calculated, %: C 48.14; H 7.71; P 9.56

3. RESULT AND DISCUSSION

The condensation reaction of phosphonoacetic aldehyde with 1,3-di-chloroacetone in the presence of potassium carbonate in DMF was studied. An oxinane derivative (1) with a phosphoryl group in the side chain was obtained in 30% yield (Scheme 1)

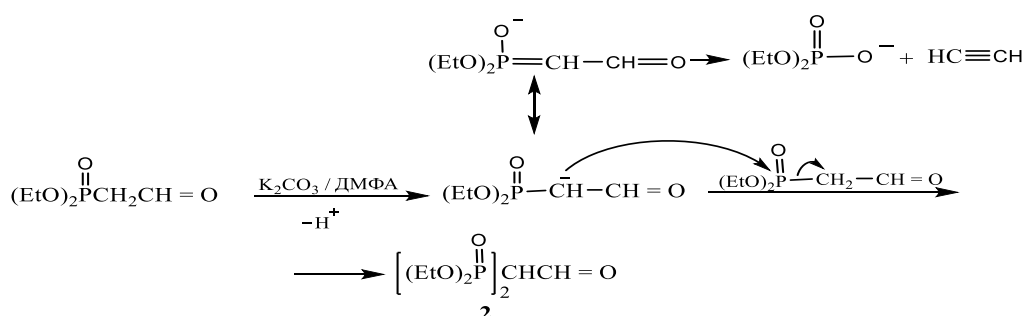


The formation of compound **1** should be considered as a product of primary alkylation of the aldehyde at the active methylene group with subsequent prototropic isomerization and O-alkylation to compound **1**



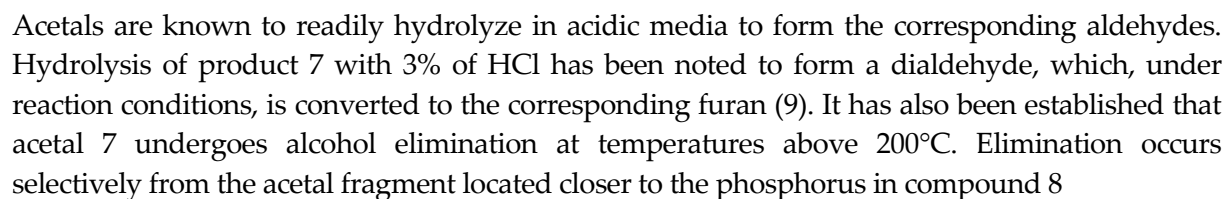
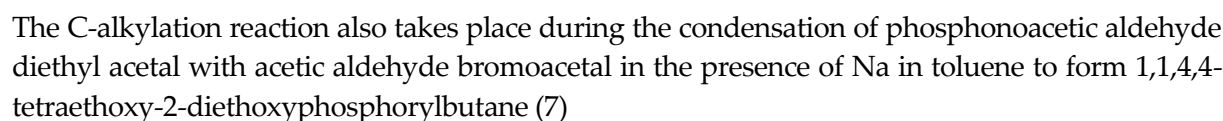
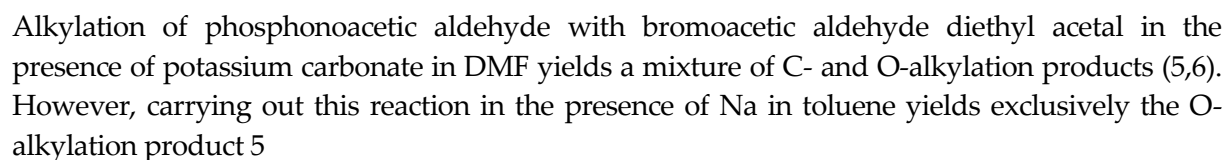
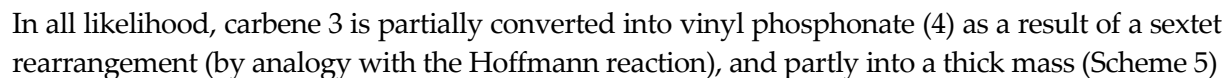
The low yield of product 1 is apparently due to alternative transformations of the substrate and reagent under the action of potash in DMFA.

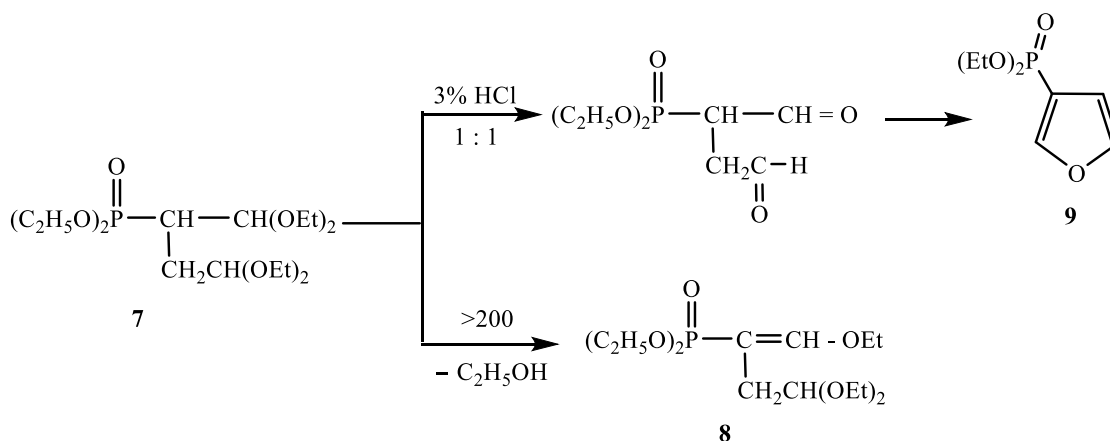
It was shown experimentally that phosphonoacetic aldehyde, under the specified conditions (K₂CO₃/DMF), undergoes a series of transformations, forming intermolecular condensation products – bis[diethoxyphosphoryl]acetic aldehyde (2) and the product of intramolecular decomposition of phosphonoacetic aldehyde with the formation of acetylene and phosphate ion (Scheme 3)



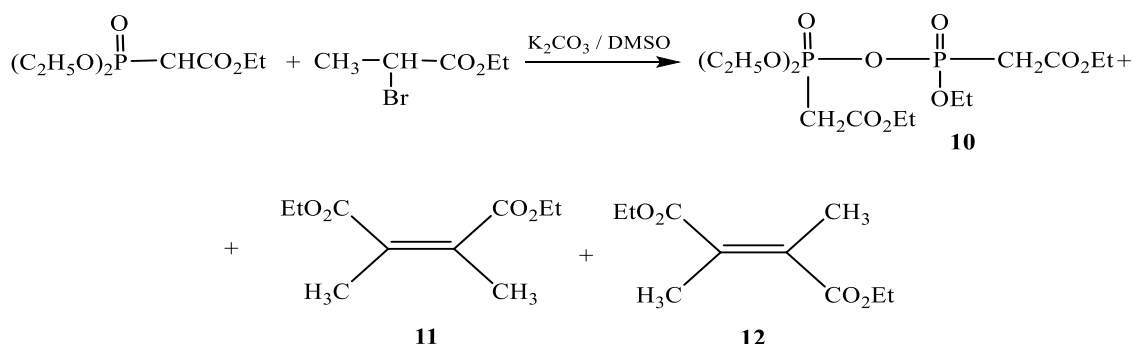
When this reaction was carried out in DMSO, dimethyl sulfone, a small amount of vinyl phosphonate (14%), and a thick residue, the structure of which could not be determined, were isolated from the reaction mixture.

Dimethyl sulfoxide acts as a nucleophilic reagent in this process, attacking the carbonyl carbon to form a bipolar ion, the decomposition of which yields dimethyl sulfone and the corresponding carbene 3



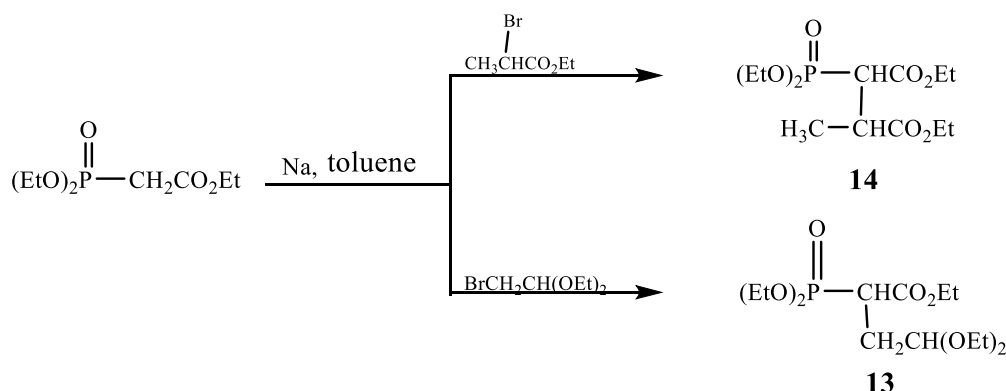


Phosphonacetates, unlike phosphonoacetaldehyde, which exhibit aldo-enol tautomerism, behave differently in condensation reactions with halogenated derivatives. Alkylation of phosphonoacetate under $\text{K}_2\text{CO}_3/\text{DMSO}$ conditions with halogenated carbonyl derivatives does not yield the desired result. Thus, the reaction of triethyl phosphonoacetate with α -bromopropionate in the presence of potassium carbonate in DMSO forms phosphonate anhydrides (10), as well as esters of maleic (11) and fumaric (12) acids

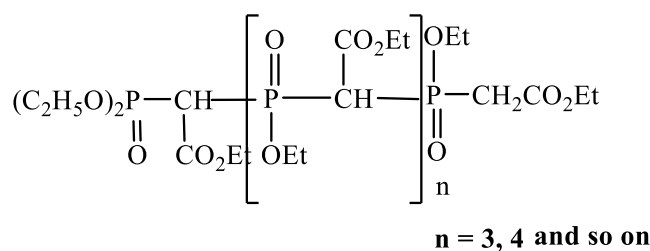


The formation of esters 11 and 12 from ethyl bromoacetate was previously discussed [20].

Phosphonoacetate, using metallic Na in toluene, is easily alkylated with ethyl α -bromopropionate and bromoacetaldehyde acetal, yielding C-alkylation products 13 and 14, respectively, in good yields.



Unlike phosphonoacetic aldehyde, which forms a carbanion in the $\text{K}_2\text{CO}_3/\text{DMSO}$ system at normal temperature, phosphonoacetate forms a carbanion only at temperatures above 100°C . Under these conditions, intermolecular condensation of the latter occurs with the formation of oligomers, which can find application in metallurgy.



In summary, it should be noted that the direction and yields of the alkylation reaction of α -phosphorylated carbonyl compounds with α -halocarbonyl derivatives are influenced by both the nature of the reactants and the nature of the solvent. It was found that in DMSO, the alkylation reactions of α -phosphorylcarbonyl compounds with halogenated carbonyl derivatives proceed predominantly with the formation of an O-alkylation product, whereas these reactions in DMF yield a mixture of C- and O-alkylation products. Low yields of the target products are due to self-condensation of the starting materials (both substrates and reactants) under the specified conditions.

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HYDROSPHERE POLLUTION BY OIL AND PETROLEUM PRODUCTS: SOURCES, IMPACTS, AND REMEDIATION METHODS

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ARTICLE INFO	ABSTRACT
Article history: Received: 2025-07-29 Received in revised form: 2025-08-16 Accepted: 2025-10-19 Available online: 2026-06-26	<i>The article is devoted to the sources of hydrosphere pollution by oil and petroleum products, their environmental impacts, and modern methods for oil spill remediation. It is shown that the main pathways of oil contamination in aquatic environments include ship discharges, port operations, industrial and municipal wastewater, river runoff, atmospheric deposition, as well as accidents involving offshore drilling platforms and vessels. The processes of oil transformation on the water surface and the factors governing its spreading and degradation are discussed. An analysis of mechanical, chemical, and sorption-based cleanup methods is presented, including the use of skimmers, containment booms, dispersants, oil collectors, and sorbents of various origins. Particular attention is given to the Corexit family of dispersants and other commercial reagents, with emphasis on their effectiveness, application limitations, and potential toxicity. Promising surfactant-based reagents and polymer-surfactant complexes capable of providing long-term localization of oil slicks are also reviewed. The study concludes that the selection of oil spill response technologies should be based on specific hydrometeorological conditions and pollution characteristics, which is especially important for the protection of the Caspian Sea ecosystem.</i>
Keywords: oil pollution; oil spills; dispersants; sorbents; surfactants	

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INTRODUCTION

Rapid economic development has led to the emergence of new technologies. Due to their efficiency and practicality, these technologies are widely used in various industrial sectors to meet growing demand. However, despite their modern design and advanced capabilities, they cannot completely eliminate the risk of accidents. As a result, industrial accidents can lead to severe environmental and economic consequences.

Approximately three-quarters of the Earth's surface is covered by water. Water is one of the most valuable, irreplaceable, and inexhaustible resources for humanity. Oceans and seas play a crucial role in the economic development of countries with direct access to marine waters. Maritime transportation, as well as the utilization of marine flora and fauna, contributes significantly to national economies.

In recent years, incidents such as mass strandings of whales and dolphins and the formation of thousands of cubic meters of foam along coastlines after storms have indicated increasing levels of water pollution. Preventing water pollution and treating contaminated water remain among

the most important global environmental challenges [1-3]. Water pollution has many causes, and consequently, various remediation methods have been developed. One of the major pollutants of aquatic environments is oil. The irrational exploitation of natural resources, together with the use of outdated technologies and equipment that fail to comply with modern technological and environmental standards during resource extraction, transportation, and processing, constitutes one of the primary sources of environmental pollution. In particular, contamination arising from oil and gas extraction, refining, and transportation activities is recognized as a major anthropogenic factor exerting adverse impacts on ecosystems and environmental quality [4-7].

It is well known that modern economic development is impossible without petroleum. Every year, between 4 and 10 million tons of oil enter the world's oceans. Depending on its viscosity and ambient temperature, spilled oil usually spreads over the water surface as a thin film several millimeters thick

The physical and chemical transformation of oil spilled into marine environments depends mainly on the oil's viscosity, water temperature, and turbulence. After oil is released onto the water surface, it undergoes a series of transformations (Figure 1).

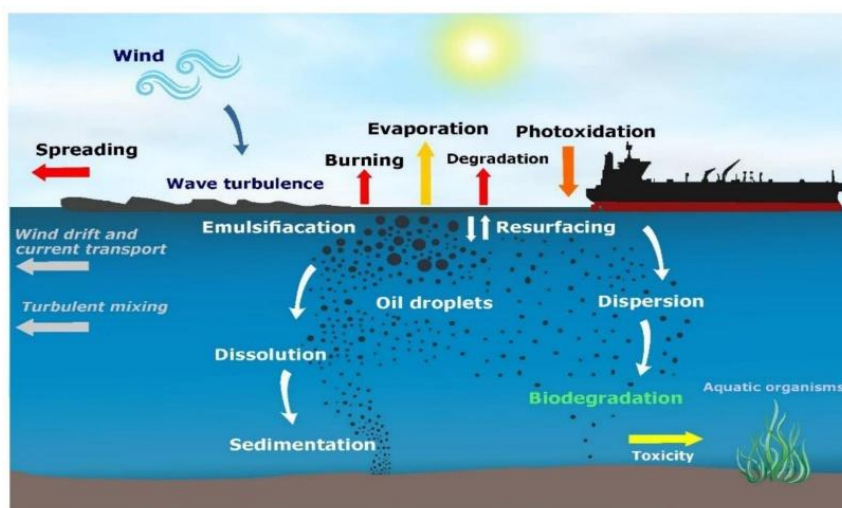


Fig. 1. Processes of Transformation Experienced by an Oil Slick on the Water Surface

Oil pollution can originate from various sources, which can be divided into two categories:

1. Continuous pollution sources
2. Accidental pollution sources

The main pathways through which oil and petroleum products contaminate water include:

- Discharge of ballast water, oily wastewater, and tank washing residues from ships (23%);
- Waste releases into ports and port waters, including losses during tanker bunkering operations (17%);
- Industrial wastewater and sewage discharges (10%);
- Stormwater runoff (5%);
- Accidents involving offshore drilling platforms and vessels (6%);
- Offshore shelf drilling activities (1%);
- Atmospheric deposition (10%);
- River runoff in various forms (28%).

During the last 30 years, nearly 2,000 wells have been drilled in the world's oceans. Since 1964, approximately 1,000 of these wells have been drilled in the North Sea alone, with around 350 production wells being developed. Small leaks from drilling platforms result in annual oil losses of approximately 0.1 million tons, while major accidents occur periodically.

A significant amount of oil reaches seas from land via domestic wastewater, stormwater, and river systems. This source contributes more than 2 million tons of oil pollution annually. In addition, industrial facilities and oil refineries discharge approximately 0.5 million tons of oil into marine environments every year.

Examples of accidental pollution sources include the 2010 oil spill in the Gulf of Mexico and tanker accidents. On April 20, 2010, during the cementing operation of an offshore oil well in the central Gulf of Mexico, an oil platform exploded and caught fire. Estimates indicate that approximately 5,000 barrels (700 tons) of oil per day leaked from the uncontrolled well into the Gulf of Mexico [8].

The methods used to remove oil from water depend on the source of contamination and the amount of oil released. Following major spills, oil begins spreading across the water surface, depending on weather conditions. Strong winds accelerate the dispersion process.

Oil spilled on water can be removed using mechanical, physical, and chemical methods. Thick oil layers are generally best removed mechanically. Mechanical recovery of oil slicks is typically performed using skimmers [9-11]. Skimmers are most productive and efficient when the oil layer thickness exceeds 10 mm.

However, during large-scale spills, weather conditions often cause oil slicks to spread over extensive areas, forming very thin films. This significantly reduces skimmer efficiency, allowing recovery of only 10–15% of the spilled oil. To improve performance, floating booms arranged in V-, J-, or U-shaped configurations are used to concentrate oil and facilitate collection. Nevertheless, strong winds substantially reduce the effectiveness of this approach.

Mechanical methods cannot effectively remove oil films thinner than 0.1 mm. After mechanical recovery, a thin residual oil layer often remains on the water surface. This layer forms a barrier between the atmosphere and hydrosphere, hindering oxygen and carbon dioxide exchange, reducing water evaporation, and limiting sunlight penetration into deeper water layers. Consequently, it has a highly detrimental effect on aquatic flora and fauna.

Surfactants for Thin Oil Film Removal

Various surfactants are widely used to remove thin oil films. According to their mode of action, these substances are classified into two groups:

1. Oil dispersants
2. Oil collectors (oil herders)

Oil Dispersants

Dispersants are sprayed onto thin oil films on the water surface. They break the oil into microscopic droplets that become distributed throughout the water column. These fine oil emulsions undergo relatively rapid biodegradation (Figure 2).

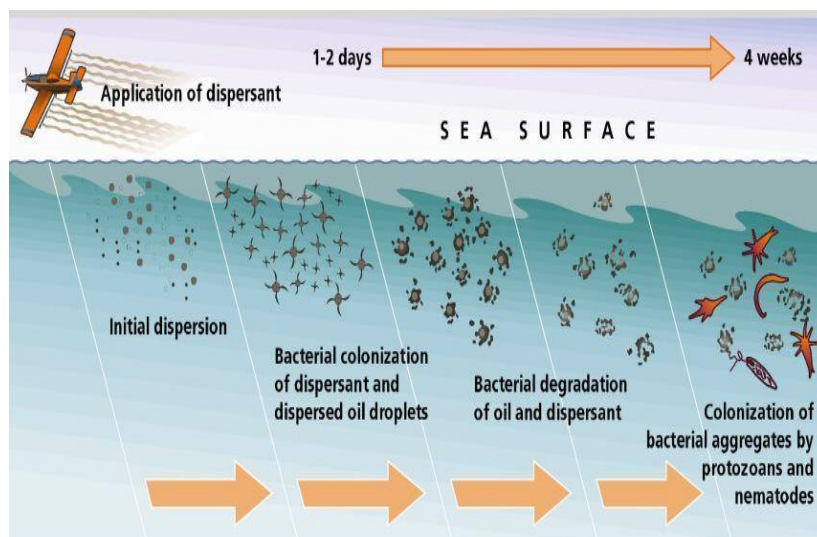


Fig. 2. Mechanism of Oil Spill Dispersion by a Dispersant on the Water Surface

Dispersants are generally most effective within 72 hours after a spill and at temperatures above 5°C. Their penetration beyond 10 meters below the water surface is undesirable. Application by aircraft or helicopters is considered most effective. Windy conditions often enhance dispersant performance, making them particularly useful when mechanical recovery is impractical.

Since dispersants exhibit some degree of toxicity, they should be applied in controlled dosages rather than excessive quantities.

One of the most widely used dispersants is Corexit, produced in several formulations by Nalco Holding Company, including:

- COREXIT 9527 [12]
- COREXIT 9580 [13]
- Corexit EC9500A [14]
- Corexit EC9527A [15]

The complete chemical composition of these products has not been fully disclosed.

Following the 2010 Deepwater Horizon disaster in the Gulf of Mexico [16], unprecedented quantities of Corexit EC9500A and Corexit EC9527A were used. Corexit EC9527A primarily contains 2-butoxyethanol, proprietary organic sulfonates, and small amounts of propylene glycol.

Corexit 9500 mainly consists of:

- Sorbitan compounds
- Succinic acid derivatives
- Petroleum distillates

Corexit EC9500A is based on hydrotreated light petroleum distillates, propylene glycol, and proprietary organic sulfonates.

The dispersant Corexit 9580 had previously been used during the 1989 Exxon Valdez oil spill in Alaska.

Other well-known dispersants include:

- Finasol OSR51 [17]
- Superdispersant 25 [18]
- Slickgone NS [19]
- Inipol IP90 [20]

The dispersing efficiency of various dispersants toward Chirag crude oil spilled on the surface of the Caspian Sea was experimentally investigated [21].

Oil Collectors and Dispersants

Oil-collecting and oil-dispersing reagents differ in raw materials, chemical structure, and properties. They can be synthesized from higher alcohols and epoxy compounds, higher fatty acids and epoxy compound, amines, orthophosphoric acid, epoxy compounds, and alkyl halides [22-27].

All dispersants can be either oil-soluble or water-soluble.

Oil-soluble dispersants generally require concentrations of 3.5% or higher, have densities lower than water, and viscosities below 50 cP.

Water-soluble dispersants contain surfactant mixtures rich in hydrophilic components and are typically used at concentrations up to 10%.

Before use, both oil- and water-soluble dispersants are commonly diluted to approximately 15% concentration with water or organic solvents.

One of the classic dispersants developed in the previous century is which produces highly dispersed oil emulsions with droplet diameters below 1 μm . Its distinctive feature is its versatility: it can function both as a dispersant and as an oil collector.

When used as a dispersant, an aqueous DN-75 solution is sprayed onto floating oil slicks. The surfactants in the formulation reduce the oil-water interfacial tension to approximately 2 mN/m, promoting the formation of fine oil emulsions that subsequently undergo rapid biodegradation.

The primary disadvantage of dispersion is that the oil remains within the aquatic environment.

When DN-75 is used as an oil collector, it is applied around the perimeter of the oil slick. It forms a stable monomolecular film on the water surface. This film increases surface tension at the seawater interface to approximately 45 mN/m, significantly higher than the oil-water interfacial tension. As a result, the reagent exerts greater spreading pressure than the oil itself, causing the slick to contract and become localized.

The reagent can concentrate dispersed oil into isolated slicks up to 6 mm thick and prevent further spreading. Successful localization and collection generally require approximately 5 kg of reagent per square kilometer of contaminated surface.

Different oil-collecting and dispersing agents exhibit varying efficiencies, toxicities, and durations of action. Compounds derived from higher alcohols often demonstrate high effectiveness but may possess moderate toxicity. Reagents synthesized from individual fatty acids can be relatively expensive.

Replacing pure higher fatty acids with acid fractions derived from natural triglycerides significantly reduces production costs while enhancing oil-collecting and dispersing performance through synergistic effects [28,29].

Polymer–Surfactant Complexes

Another important class of oil spill response agents consists of polymer–surfactant complexes. These materials differ from conventional surfactant-based reagents in several respects [30–32].

Their effect on oil slicks develops more gradually; however, they are capable of maintaining localized oil accumulations for significantly longer periods than conventional surfactants.

Sorbent-Based Cleanup

Another widely used oil spill remediation method is sorption. Sorbents can be classified into three categories [33–36]:

1. Natural sorbents (cotton, peat, sawdust, perlite, clay, etc.);
2. Artificial sorbents;
3. Synthetic sorbents.

Plant-based sorbents can absorb up to twenty times their own weight in oil and may achieve removal efficiencies as high as 99%.

Conclusion

The Caspian Sea is one of Azerbaijan's most valuable natural resources. A portion of Azerbaijan's oil production originates from offshore wells located in the Caspian Sea. In addition, the Caspian Sea serves as an important transportation route for crude oil from Central Asia to Europe.

These activities inevitably contribute to oil contamination of the Caspian Sea. In order to minimize the environmental impacts of existing and future pollution events, it is essential to apply appropriate oil spill response technologies based on a thorough assessment of the specific conditions. The implementation of mechanical, chemical, and sorption-based cleanup methods plays a critical role in protecting marine ecosystems and reducing the ecological consequences of oil pollution.

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OPTIMIZATION OF THE SYNTHESIS OF 3-FORMYL-4-HYDROXYBENZOIC ACID: A HIGH-YIELD PROTOCOL FOR A KEY BIOACTIVE BUILDING BLOCK

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ARTICLE INFO	ABSTRACT
Article history: Received: 2025-09-23 Received in revised form: 2025-10-11 Accepted: 2025-11-15 Available online: 2026-06-26	3-Formyl-4-hydroxybenzoic acid is an important aldehyde precursor widely used in the synthesis of biologically active thiosemicarbazone ligands and transition metal complexes. In this study, an optimized and cost-effective synthetic route for 3-formyl-4-hydroxybenzoic acid was developed using a modified Duff reaction. The reaction conditions, reagent ratios, and hydrolysis parameters were systematically optimized to improve reproducibility while minimizing raw material consumption. The target compound was obtained in 38% yield using significantly lower quantities of starting materials compared to previously reported methods. The synthesized compound was comprehensively characterized by FTIR, ¹ H NMR, and ¹³ C NMR spectroscopy. The developed protocol provides an economical and practical approach for obtaining high-purity aldehyde precursors suitable for further applications in coordination chemistry and anticancer metallodrug development.
Keywords: Duff reaction; thiosemicarbazone; aldehyde synthesis; bioactive ligands; anticancer agents	

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1. INTRODUCTION

Cancer remains one of the most serious global health problems in modern medicine. According to the GLOBOCAN 2022 report, approximately 20 million new cancer cases and 9.7 million cancer-related deaths were recorded worldwide within a single year [1]. The severe side effects and limited selectivity associated with conventional chemotherapeutic agents have accelerated research toward transition metal complexes as alternative anticancer agents with improved biological activity and selectivity [2].

Among the various ligand systems investigated in medicinal inorganic chemistry, thiosemicarbazones (TSCs) have attracted considerable attention due to their broad spectrum of biological activities, including antiviral, antibacterial, antifungal, and particularly antitumor properties [3-5].

The biological performance of TSC-based metal complexes is strongly dependent on the structural and electronic characteristics of the ligand framework. Therefore, the efficient synthesis of functionalized aldehyde precursors plays a crucial role in the development of next-generation metallodrugs [6-8].

In this context, 3-formyl-4-hydroxybenzoic acid represents a strategically important precursor for the preparation of water-soluble thiosemicarbazone ligands. The presence of the carboxylic acid functionality enhances water solubility and bioavailability, which are critical parameters in drug design. However, literature reports reveal substantial inconsistencies regarding the synthesis of this compound. Some methods provide relatively low yields of approximately 19% [9], whereas other protocols reporting yields near 40% require large-scale reagent consumption and complicated purification procedures [10]. Such limitations reduce the practical applicability and scalability of the synthesis.

Additionally, the high commercial price of 3-formyl-4-hydroxybenzoic acid significantly limits its accessibility for many research laboratories. Consequently, the development of an economical, reproducible, and efficient synthetic route remains highly desirable.

The primary objective of the present study was to optimize the synthesis of 3-formyl-4-hydroxybenzoic acid through a modified Duff reaction by carefully adjusting reaction parameters and reagent ratios. The developed method successfully afforded the target aldehyde in a reproducible 38% yield using substantially lower amounts of starting materials. The synthesized compound was thoroughly characterized using FTIR, ^1H NMR, and ^{13}C NMR spectroscopy. This optimized protocol establishes a practical foundation for the future synthesis of biologically active thiosemicarbazone-metal complexes.

2. MATERIALS AND EXPERIMENTAL METHODS

2.1. Materials

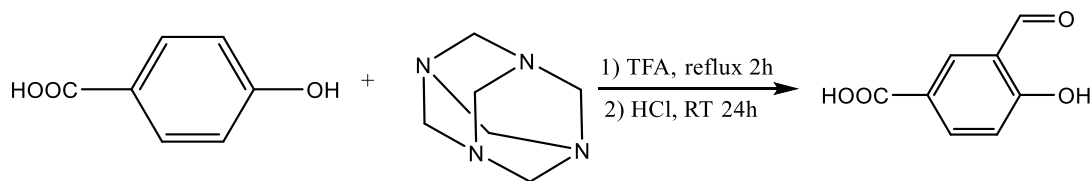
All chemicals and solvents were obtained from commercial suppliers and used without further purification unless otherwise specified. 4-Hydroxybenzoic acid, hexamethylenetetramine, trifluoroacetic acid (TFA), hydrochloric acid, sodium sulfate, and organic solvents were purchased from Sigma-Aldrich and Merck.

2.2. Synthesis of 3-formyl-4-hydroxybenzoic acid

The synthesis of 3-formyl-4-hydroxybenzoic acid was carried out using a modified Duff reaction (Scheme 1). In a typical experiment, 4-hydroxybenzoic acid (0.75 g, 5.43 mmol) was suspended in 2.5 mL of trifluoroacetic acid (TFA). This suspension was added dropwise to a solution of hexamethylenetetramine (0.78 g, 5.5 mmol) dissolved in TFA under continuous stirring.

The reaction mixture was refluxed for 2 h under a nitrogen atmosphere to minimize oxidative side reactions. After completion of the reaction, the mixture was cooled to room temperature and hydrolyzed using 75 mL of 4 M hydrochloric acid under vigorous stirring for 3 h.

The resulting yellow precipitate was filtered, washed thoroughly with cold distilled water, and dried. The crude product was dissolved in diethyl ether and extracted. The organic phase was dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was removed under reduced pressure. The target compound was obtained as a yellow crystalline powder (0.35 g, 38% yield, m.p. 247.3–249.1 °C).



Scheme 1. Synthesis of 3-Formyl-4-hydroxybenzoic acid.

3. RESULTS AND DISCUSSION

3.1. Synthesis and Process Optimization

In this study, 3-formyl-4-hydroxybenzoic acid was successfully synthesized using an optimized Duff reaction protocol. Previous literature reports demonstrated significant variability in reaction yields. Sardroud et al. reported yields of approximately 19% for structurally related aldehydes, whereas Irfan et al. achieved higher yields using substantially larger quantities of starting materials and more labor-intensive purification procedures.

The major achievement of the present work lies in the optimization of reagent ratios, reaction atmosphere, and hydrolysis conditions, enabling a reproducible yield of 38% while minimizing reagent consumption. The use of a nitrogen atmosphere effectively reduced possible oxidative side reactions, whereas controlled hydrolysis conditions improved product formation and isolation.

The developed method offers several advantages, including lower material consumption, simplified work-up procedures, improved reproducibility, and reduced overall synthesis cost. These improvements make the proposed protocol particularly suitable for future applications involving ligand synthesis and coordination chemistry.

Table 1. Comparison of synthetic parameters and yields for 3-formyl-4-hydroxybenzoic acid.

Method / Reference	Starting Material (Amount)	Reaction Conditions	Yield (%)	Observations / Limitations
Sardroud et al. (2020)	4-Hydroxybenzoic acid (22 mmol, 3.0 g)	Modified Duff Reaction / Argon	~19%	Reported significant yield inconsistencies and lower efficiency for the target aldehyde.
Irfan et al. (2016)	4-Hydroxybenzoic acid (108 mmol, 15 g)	Duff Reaction / High reagent volume	~40%	Achieved slightly higher yields but required substantially larger quantities of reagents.
This Work (Optimized)	4-Hydroxybenzoic acid (5.43 mmol, 0.75 g)	Modified Duff / N ₂ atm / Controlled hydrolysis	38%	Highly reproducible; minimized raw material consumption; cost-effective alternative to commercial sources.

3.2. Spectroscopic Characterization

The synthesized compound was structurally characterized using FTIR, ¹H NMR, and ¹³C NMR spectroscopy.

FTIR Analysis

In the FTIR spectrum, the strong absorption band observed at approximately 1672 cm⁻¹ was assigned to the aldehyde carbonyl (C=O) stretching vibration, while a distinct peak near 1700 cm⁻¹ confirmed the presence of the carboxylic acid C=O group. A broad and intense absorption

band centered in the 3300–2500 cm^{-1} region corresponded to the characteristic O-H stretching of the carboxylic acid, overlapping with the phenol O-H stretch observed around 3200 cm^{-1} . This broadness indicates extensive intermolecular hydrogen bonding within the structure.

Additionally, the aldehyde group was further confirmed by the characteristic C-H stretching vibrations appearing at 2850 cm^{-1} and 2750 cm^{-1} . The skeletal vibrations of the aromatic ring were clearly identified by the multiple C=C stretching bands located at approximately 1600, 1500, and 1450 cm^{-1} , supporting the presence of the aromatic framework in the synthesized compound.

FTIR (ATR) ν (cm^{-1}): 3300-2500 (O-H), 3200 (O-H), 2850-2750 (C-H_{ald}), 1700 (C=O_{acid}), 1680 (C=O_{ald}), 1600, 1500, 1450 (C=C_{ar}).

^1H NMR Analysis

The ^1H NMR spectrum (400 MHz, DMSO- d_6) provided clear confirmation of the target structure. The characteristic aldehyde proton appeared as a sharp singlet at δ 10.29 ppm. The hydroxyl and carboxylic acid proton signals were observed as a broad singlet at δ 11.52 ppm.

The aromatic region displayed three characteristic proton signals consistent with the substitution pattern of the aromatic ring. A doublet at δ 8.23 ppm (J = 2.3 Hz, 1H) was assigned to the proton at the C-2 position. A doublet of doublets at δ 8.03 ppm (J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1H) corresponded to the C-6 proton, while the doublet at δ 7.07 ppm (J = 8.7 Hz, 1H) was attributed to the C-5 proton.

^1H NMR (400 MHz, DMSO- d_6): δ 11.52 (s, 1H), 10.29 (s, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.03 (dd, J = 8.7, 2.3 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H) ppm.

^{13}C NMR Analysis

The ^{13}C NMR spectrum (100 MHz, DMSO- d_6) further confirmed the molecular structure. Signals observed at δ 195.53 ppm and δ 169.21 ppm were assigned to the aldehyde and carboxylic acid carbonyl carbons, respectively. The resonance at δ 164.81 ppm corresponded to the aromatic carbon attached to the hydroxyl substituent.

Additional aromatic carbon signals were observed in the range of δ 123.75–135.56 ppm, consistent with the expected aromatic framework of the synthesized compound.

^{13}C NMR (100 MHz, DMSO- d_6): δ 195.53, 169.21, 164.81, 135.56, 133.20, 123.80, 123.75 ppm.

3.3. Potential Applications in Anticancer Metal Complexes

The synthesized aldehyde precursor is highly suitable for the preparation of biologically active thiosemicarbazone ligands and transition metal complexes. The presence of the carboxylic acid group is expected to improve the water solubility and bioavailability of the resulting metal complexes.

Previous studies have demonstrated that water-soluble thiosemicarbazone-metal complexes exhibit enhanced biological activity and improved pharmacological properties. Therefore, the optimized synthetic protocol developed in this work provides a valuable foundation for future studies involving Cu(II), Ni(II), and Zn(II)-based anticancer complexes.

4. CONCLUSION

In the present study, an optimized and cost-effective synthetic route for 3-formyl-4-hydroxybenzoic acid was successfully developed using a modified Duff reaction. The optimization of reaction conditions, reagent ratios, and hydrolysis parameters enabled the reproducible synthesis of the target compound in 38% yield while significantly reducing raw material consumption compared to previously reported methods.

The synthesized aldehyde was thoroughly characterized by FTIR, ^1H NMR, and ^{13}C NMR spectroscopy, confirming the successful formation of the desired structure. The obtained spectroscopic data were consistent with the proposed molecular structure and demonstrated the presence of the aldehyde, hydroxyl, and carboxylic acid functional groups.

The developed protocol provides several practical advantages, including lower synthesis cost, simplified purification, improved reproducibility, and reduced chemical waste generation. These improvements make the method suitable for future laboratory-scale and preparative applications.

Moreover, the synthesized compound represents an important precursor for the preparation of biologically active thiosemicarbazone ligands and transition metal complexes with potential anticancer activity. Therefore, the present work establishes a useful and accessible synthetic foundation for future studies in medicinal inorganic chemistry and metallodrug development.

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PROSPECTS FOR THE DEVELOPMENT OF RESEARCH IN THE FIELD OF DESIGNING EFFICIENT ION EXCHANGERS

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Article history: Received: 2025-11-08 Received in revised form: 2025-11-21 Accepted: 2025-12-22 Available online: 2026-06-26 Keywords: furfural, furan compounds, thiourea, phosphoric acid derivatives, polysilica acid, DAA, KOH, cations, oligo(polymer), molecular weight, vinylacetylene, sodium tripolyphosphate, IR spectrum, dimethylformamide, chromatography-mass spectrometry.	The article emphasizes the importance of using furfural, phosphoric acid, and thiourea as the main monomers in the synthesis of ion exchangers. Based on this approach, the synthesis of new ion-exchange polymers derived from furfural as a secondary raw material is presented, along with the study of their sorption and operational properties, determination of the molecular weight of the resulting ion exchanger, and a description of the method for its preparation. Identifying effective and practical applications of these materials for the treatment of industrial and purified waters in various chemical industry processes, including hydrometallurgy, holds significant scientific, technical, and practical importance.

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1. INTRODUCTION

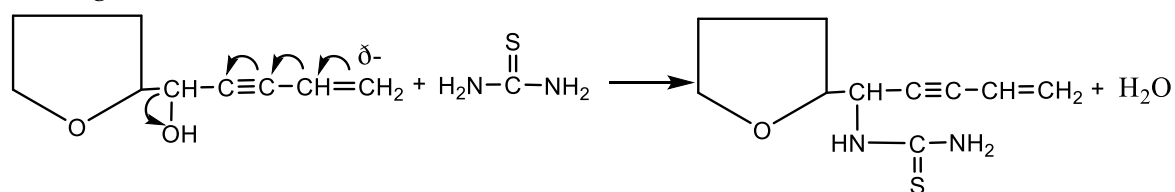
In recent years, the development of materials and compositions with desired properties containing phosphate groups has gained increasing importance. Phosphate-containing natural compounds are components of widely used medicinal pharmaceuticals. Compounds with phosphate groups form the foundation not only of inorganic chemistry but also of living organisms. The ease of modification of the phosphate group in organic compounds is of both practical and theoretical significance and has attracted considerable interest among researchers. At present, the scale of industrial organic synthesis is so large that the issue of limited natural oil and gas resources required to meet these demands remains relevant. In this context, the production of key compounds from naturally renewable raw materials is considered a promising direction [1-3].

Modern advances in science and technology have made it possible to create a new class of polymeric composite materials formed from a combination of components of different chemical nature, which significantly surpass the properties of the individual starting components. In terms of their overall composite characteristics, they exhibit distinctive physicochemical, magnetic, and optoelectronic properties, as well as high chemical and thermal stability and enhanced resistance to various types of radiation. In recent years, furan derivatives have gained increasing importance in the development of materials and compositions with predetermined

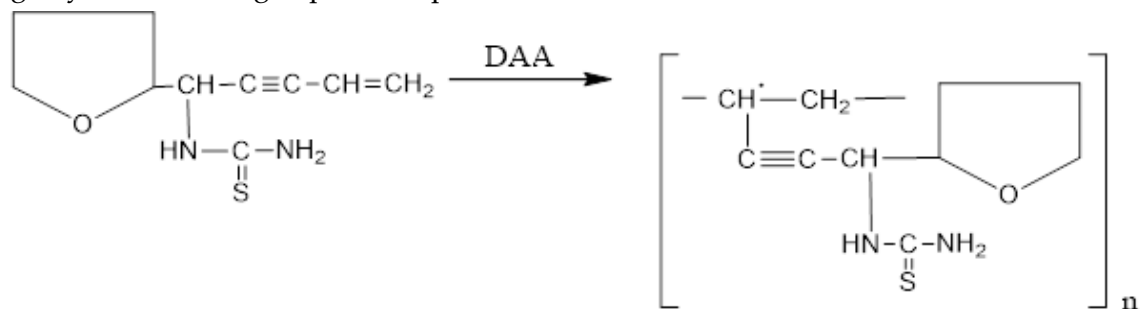
properties [4-6]. Inorganic sorbents, such as metal (IV) phosphates, are promising materials for the separation of various ions, particularly alkali metal cations that are difficult to isolate by other methods, as well as for deep purification [7]. These ion-exchange materials are characterized by high radiation resistance and the ability to sorb alkali metal cations, making them suitable for applications in the nuclear industry. The ability to selectively absorb a range of cations from a mixture containing a large number of competing ions is also of significant importance. To ensure good mixing of thiourea with the reaction medium and the formation of a homogeneous system, it was first dissolved in a small amount of hot ethanol [8-10]. Then, 1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-ol was added dropwise using a separatory funnel. After achieving an equimolar ratio, a few drops of acid (e.g., 0.1 M HCl or H₂SO₄) were added to the mixture, and it was heated at 50–60 °C for 1–2 hours. As a result, a condensation reaction occurred, forming a C–N bond and releasing water, which could be observed visually. During the reaction, under the influence of these chemical interactions, 1-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiourea was obtained. [11-13].

2. EXPERIMENTAL PART

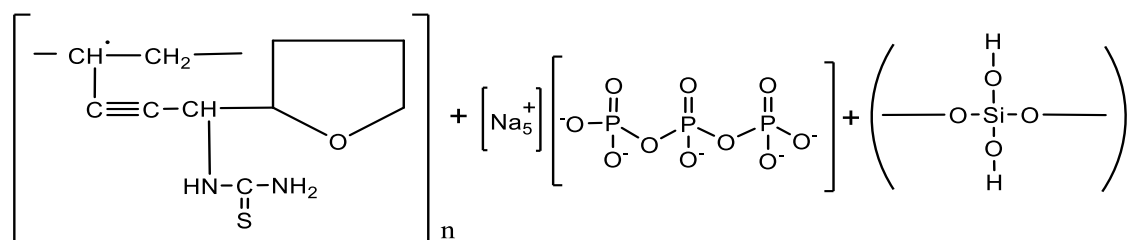
First, thiourea reacts with the hydroxyl group of the intermediate compound according to the following scheme.



The resulting intermediate compound undergoes polymerization. The reaction proceeds in a single system following a specific sequence.



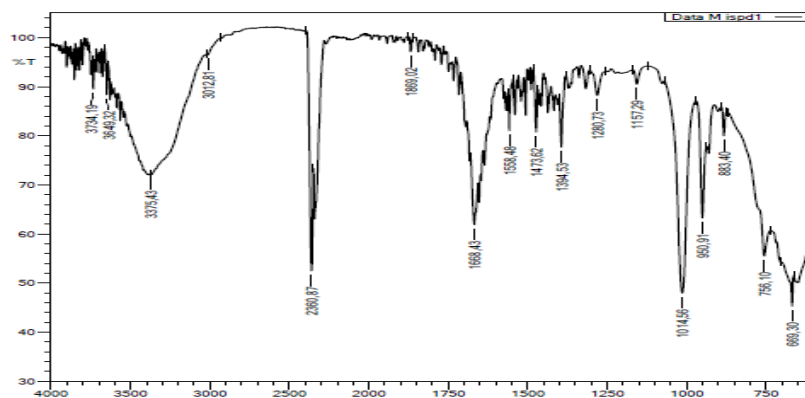
To increase the number of active centers and electron pairs in the polymer, as well as to ensure mechanical strength, sodium tripolyphosphate was used, and the process can generally be described as follows.



Viscosity Polyphos-1

Viscosity dPa/s	Temperature °C
1.8	100
2.5	80
3.5	60
4.5	45
5.5	30
6.2	20
7.2	10
8.5	2

In the presence of a strongly alkaline system, the reaction time and product yield depend on the temperature, reaching up to 74 %. A range of modern physicochemical methods was used to identify the synthesized compounds. To characterize the bonds within the substances, IR spectroscopy was employed.



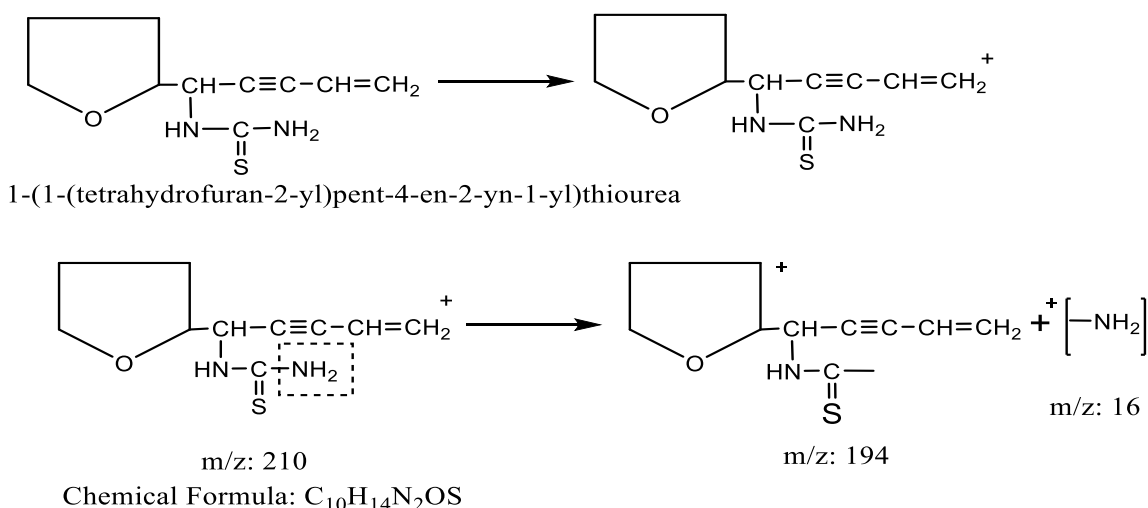
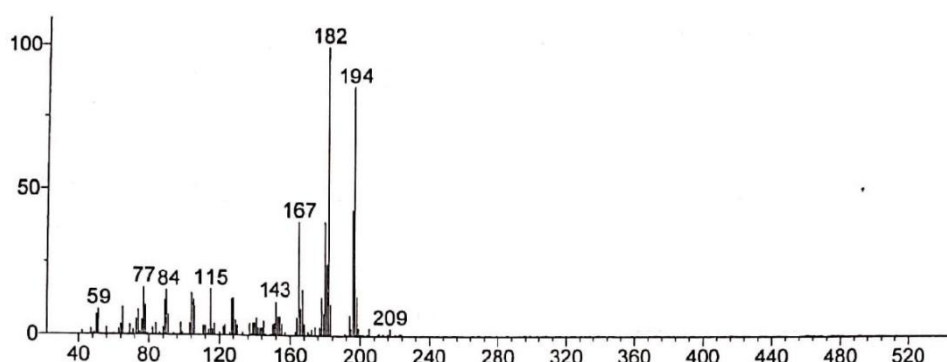
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For the amino group -NH_2 in thiourea, two absorptions are observed in the region $3400\text{--}3200\text{ cm}^{-1}$; for the thiocarbonyl group -C=S , in the region $1400\text{--}1100\text{ cm}^{-1}$; the deformation vibration of the $\text{-C}\equiv\text{C-}$ group is recorded at 2120 cm^{-1} ; for the secondary bond RHC=CH_2 — 1645 cm^{-1} ; for the carbonyl group C=O — 1668.43 cm^{-1} ; for C=S — 1014.56 cm^{-1} ; for the C-H bond — 756.10 cm^{-1} ; for the unsaturated acetylene group — 1869.02 cm^{-1} ; for the furan ring — $1558\text{--}1474\text{ cm}^{-1}$; and for the aromatic C=C bond — $1281\text{--}1157\text{ cm}^{-1}$.

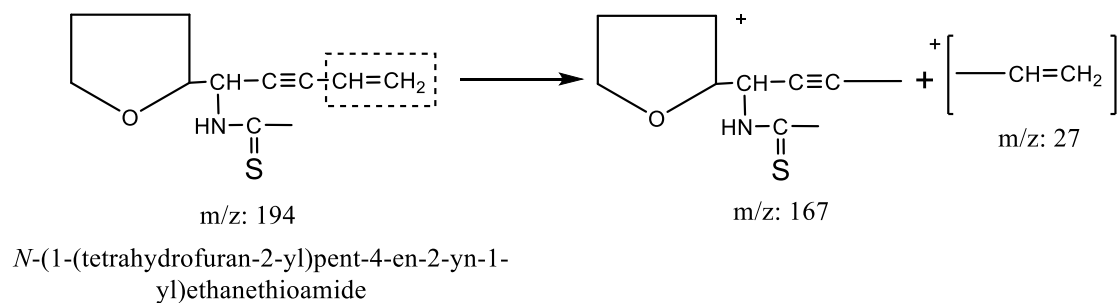
Additionally, the structure of the new compound can be inferred from the fragmentation sequence in the chromatograph–mass spectrum. After introducing 1-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiourea into the chromatograph–mass spectrometer, under the selected conditions, the molecular ion of 1-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiourea with m/z 210 was detected in the retention time range of 10.639 to 10.708 minutes.

** Search Report Page 1 of 1 **

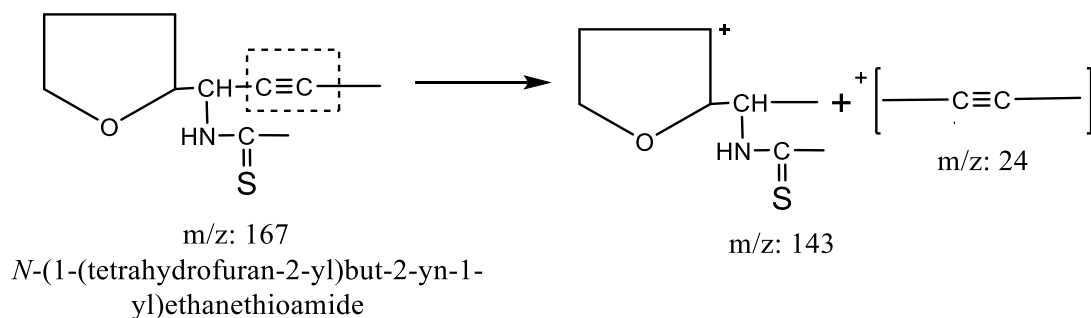
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Compound in Library Factor = -342



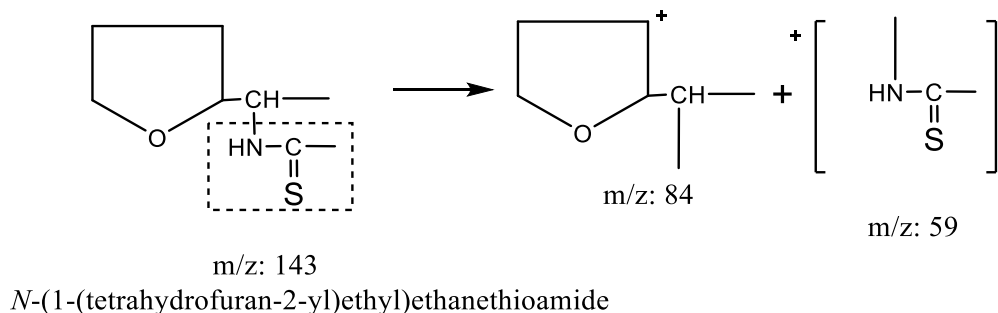
Additionally, the spectrum showed the formation of fragment ions with m/z 209, m/z 194, m/z 167, m/z 143, m/z 84, and m/z 59. At 10.639 minutes, the loss of a hydroxyl (-OH) radical from the 1-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiourea ion resulted in the formation of the m/z 194 ion. This peak corresponds to the N-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) ethanethioamide ion and is consistent with the associated bond energies.



From the tertiary *N*-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) ethanethioamide ion, the loss of a methylene radical results in the formation of the m/z 167 ion. This peak corresponds to *N*-(1-(tetrahydrofuran-2-yl) -2-yn-1-yl) ethanethioamide.



In turn, from the *N*-(1-(tetrahydrofuran-2-yl) but-2-yn-1-yl) ethanethioamide ion, at 10.708 minutes, the loss of radicals resulted in the formation of the m/z 59 ion.



At the end of the analysis, the kinetics of the resulting *N*-(1-(tetrahydrofuran-2-yl) ethyl) ethanethioamide ions occur in accordance with the complexity of ring opening. In the initial stage, the cleavage of ions from the side chain, followed by the fragmentation of the ring, confirms the correctness and precise identification of the compound's structure, consistent with the observed fragmentation patterns.

3. CONCLUSION

Using polysilicic acid and the sol-gel method, organic-inorganic hybrid composites were obtained with the involvement of the vinylfurfuryl thiourea sodium tripolyphosphate copolymer. The structure of the composites is formed by a three-dimensional silica dioxide matrix with tightly integrated organic copolymers, which provides them with high thermal and chemical stability. New copolymers based on the system 1-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiourea were synthesized via radical copolymerization in DMSO solution at 85 °C in the presence of an initiator for 3 hours, achieving a yield of 74 %. The hybrid composites based on 1-

(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiourea, sodium tripolyphosphate, and polysilicic acid exhibit high sorption activity toward calcium, magnesium, copper, nickel, and iron ions in both acidic and alkaline media. Chromatography-mass spectrometry identified the molecular ion of 1-(1-(tetrahydrofuran-2-yl) pent-4-en-2-yn-1-yl) thiomochelavin, confirmed its complete structure through the fragmentation sequence, and demonstrated that the resulting fragment ions correspond to the unambiguous identification of the compound.

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HYDRAZONE DERIVATIVES AS ANTIFUNGAL AGENTS: SYNTHESIS, BIOLOGICAL EVALUATION AND MOLECULAR DOCKING STUDIES

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Article history: Received:2025-10-30 Received in revised form:2025-11-10 Accepted:2025-12-15 Available online:2026-06-26 Keywords: hydrazine derivatives, antifungal agents, in silico analysis	Hydrazone derivatives are an important class of compounds known for their diverse biological activities, including antifungal properties. In the present study, six hydrazone derivatives were evaluated for their antifungal activity against <i>Candida albicans</i>, <i>Candida guilliermondii</i>, and <i>Candida tropicalis</i> using the agar well diffusion method. In addition, molecular docking studies were performed to investigate their interactions with <i>Candida albicans</i> lanosterol 14α-demethylase (CYP51, PDB ID: 5TZ1), a key enzyme involved in ergosterol biosynthesis. The biological results demonstrated that all tested compounds exhibited antifungal activity, although their effectiveness varied depending on the fungal species. Among the investigated derivatives, (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine showed the strongest inhibitory effect, producing inhibition zones of 26.3 ± 1.0 mm, 26.0 ± 0.9 mm, and 27.0 ± 0.6 mm against <i>C. albicans</i>, <i>C. guilliermondii</i>, and <i>C. tropicalis</i>, respectively. Its activity was found to be 1.2–1.4 times higher than that of the reference drug fluconazole. <i>Candida albicans</i> exhibited the highest sensitivity toward all tested compounds. Molecular docking analysis revealed that the selected hydrazone derivatives were accommodated within the CYP51 active site and formed stabilizing interactions with key amino acid residues, including LYS358, LEU340, GLU336, GLU339, and GLU343. Compound I exhibited the most favorable docking score (-4.7 kcal/mol), while Compounds II and VI displayed comparable binding modes and interaction patterns. Hydrogen bonding, hydrophobic contacts, and π-mediated interactions contributed to ligand stabilization within the binding pocket. The combined experimental and computational findings suggest that hydrazone derivatives, particularly (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine, represent promising scaffolds for the development of novel antifungal agents against <i>Candida</i> infections.

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1. INTRODUCTION

Hydrazones constitute an important class of nitrogen-containing organic compounds characterized by the presence of the azomethine moiety ($-\text{C}=\text{N}-\text{N}-$), which is generally formed through

the condensation of hydrazines or hydrazides with aldehydes and ketones [1-3]. The azomethine linkage imparts unique electronic properties to these molecules, while the presence of adjacent nitrogen atoms allows hydrazones to exhibit both nucleophilic and electrophilic behavior, making them highly versatile synthetic intermediates [3-4]. Furthermore, many hydrazone derivatives exist in keto–enol tautomeric forms, which significantly influence their reactivity, coordination ability, and biological activity [2, 3]. The most common synthetic route involves the reaction of substituted hydrazides or hydrazines with carbonyl compounds in alcoholic media such as ethanol or methanol, frequently in the presence of catalytic acetic acid, affording the target products in high yields under relatively mild reaction conditions [1,2]. This synthetic methodology is particularly attractive because of its operational simplicity, broad substrate scope, cost-effectiveness, and excellent tolerance toward a variety of functional groups. Moreover, the condensation approach enables straightforward structural modification of both reaction partners, providing rapid access to structurally diverse hydrazones for further biological and physicochemical investigations [1]. Owing to these advantages, hydrazones have emerged as valuable synthons for the preparation of numerous heterocyclic systems and functional materials, while also serving as important pharmacophores in medicinal chemistry. Indeed, a wide range of hydrazone derivatives have demonstrated antimicrobial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, and enzyme-inhibitory activities, highlighting their significance in contemporary drug discovery and development [5-8]

The continuing emergence of multidrug-resistant pathogens has intensified the search for new bioactive molecules with improved efficacy and safety profiles. In this regard, hydrazone derivatives have attracted significant attention owing to their remarkable diversity of biological activities and their ability to serve as privileged scaffolds in medicinal chemistry [9]. Numerous studies have demonstrated that hydrazones exhibit a broad spectrum of pharmacological properties, including antimicrobial, antibacterial, antifungal, antiviral, antitubercular, anti-inflammatory, analgesic, antimalarial, anticonvulsant, anticancer, cardioprotective, and antiparasitic activities [10-12]. Furthermore, the hydrazone pharmacophore has been extensively utilized in the design of novel therapeutic agents because the azomethine ($-\text{NHN}=\text{CH}-$) linkage can interact efficiently with a variety of biological targets, while structural modifications around the hydrazone framework allow fine-tuning of biological responses [9, 13]. Among the various pharmacological applications of hydrazones, their antimicrobial properties have been investigated most extensively, reflecting the urgent need for new agents capable of combating resistant bacterial and fungal infections. Particularly, hydrazone derivatives have demonstrated promising antifungal activity against a range of clinically important fungal pathogens, including *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida tenuis*, *Cryptococcus neoformans*, *Aspergillus flavus*, and *Aspergillus niger* [13]. The antifungal potential of these compounds is often associated with the presence of the azomethine moiety and the possibility of introducing different electron-donating or electron-withdrawing substituents, which can significantly influence their interaction with fungal cellular targets. Consequently, hydrazones continue to represent a highly promising class of compounds for the development of novel antifungal agents aimed at overcoming the limitations of currently available therapies and addressing the growing challenge of fungal resistance.

Despite the considerable progress achieved in antifungal chemotherapy, the emergence of resistant fungal strains and the limited number of available therapeutic targets continue to present major clinical challenges. Consequently, the search for novel antifungal agents with

improved efficacy and safety profiles has become an important area of medicinal chemistry research. In recent years, molecular docking has emerged as a valuable computational tool for investigating ligand–target interactions and predicting the binding affinity of biologically active compounds toward specific fungal proteins [14]. By providing insights into the molecular basis of antifungal activity, docking studies facilitate the identification of key pharmacophoric features and support the rational design of more potent derivatives. Hydrazone-based compounds have attracted particular attention in this regard because their structural diversity, ease of functionalization, and ability to participate in hydrogen bonding and hydrophobic interactions make them suitable candidates for interaction with fungal enzymes and receptors. Several studies have reported that hydrazone derivatives exhibiting promising antifungal activity against *Candida albicans*, *Aspergillus niger*, and *Aspergillus flavus* also demonstrate favorable binding interactions with biologically relevant targets in molecular docking analyses, highlighting the usefulness of combining biological screening with computational approaches in the development of new antifungal agents [15–18].

Therefore, the present study focuses on the synthesis of novel hydrazone derivatives and the evaluation of their antifungal potential through molecular docking investigations. Particular attention was directed toward elucidating the relationship between structural features and predicted ligand–target interactions in order to identify promising antifungal candidates for further biological studies.

2. MATERIAL AND METHODS

2.1. Antifungal Activity

The antifungal activity of hydrazone derivatives: (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine (I); (E)-1-(4-chlorobenzylidene)-2-(4-methoxyphenyl)hydrazine (II); (E)-1-(4-nitrobenzylidene)-2-phenylhydrazine (III); (E)-1-(4-chlorobenzylidene)-2-(4-nitrophenyl) hydrazine (IV); (E)-1-(4-chlorobenzylidene)-2-phenylhydrazine (V) and (E)-1-(4-chlorobenzylidene)-2-(p-tolyl)hydrazine (VI) were tested against conditionally pathogenic yeasts of the genus *Candida* (*C. albicans* BDU MI-44, *C. guilliermondii* BDU-217, and *C. tropicalis* BDU LK-30). All test cultures were obtained from the culture collection of the Microbiology and Virology Research Laboratory of Baku State University. The antifungal activity of this compound was tested *in vitro* using the agar well diffusion method [19]. One microliters of a fresh 24-hour culture suspension (4.0 McFarland) of each test strain were aseptically distributed over the surface of the agar medium. Then, 8-mm diameter wells were made in the agar, each filled with 150 microliters of a 0.1% solution of the test compound. Yeast cultures were incubated on Sabouraud dextrose agar (Liofilchem srl, Italy) at 30°C for 48 hours. The antifungal activity was assessed by measuring the diameter (in mm) of the inhibition zone formed around the wells after incubation. DMSO (solvent) was used as a negative control, and fluconazole (antibiotic) - as positive control.

All the experiments were carried out in four replicates, and results are expressed as mean $\pm$ standard error. Statistical significance was evaluated using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Differences were considered statistically significant at $p < 0.05$.

2.2. Molecular Docking Analysis

2.2.1. Ligand preparation

Proper ligand preparation, including structure standardization, hydrogen addition, geometry optimization, charge assignment, and rotatable bond definition, is essential for obtaining reproducible docking results. The SMILES codes of the investigated compounds were obtained using ChemDraw Professional 16.0. Ligand structures were generated and energy-minimized using Chem3D 16.0. Subsequently, the optimized ligands were prepared for docking in AutoDockTools 1.5.6 through the addition of hydrogen atoms, assignment of Gasteiger charges, and definition of rotatable bonds, followed by conversion into PDBQT format. Hydrogen atoms were added and Gasteiger charges were assigned during ligand preparation. However, exhaustive protonation-state and tautomer enumeration at physiological pH was not performed; therefore, the dominant prepared structures were used consistently throughout the docking workflow.

2.2.2. Protein preparation

Protein preparation is a critical step in docking workflows because missing atoms, incorrect protonation states, crystallographic waters, and unresolved residues may substantially influence predicted ligand binding. The crystal structure of *Candida albicans* lanosterol 14 α -demethylase (CYP51) complexed with an antifungal inhibitor (PDB ID: 5TZ1) [20] was retrieved from the RCSB Protein Data Bank. Prior to molecular docking studies, the protein structure was prepared using AutoDock Tools (ADT, version 1.5.6). All crystallographic water molecules and non-essential heteroatoms were removed from the protein structure. Polar hydrogen atoms were subsequently added, and Kollman charges were assigned to all amino acid residues. To avoid errors associated with metal parameterization during docking calculations, the iron atom of the heme prosthetic group was removed before receptor preparation. The prepared protein structure was then converted into the PDBQT format required for AutoDock Vina calculations. The resulting receptor model was used for all subsequent docking simulations. The docking grid was centered on the binding site of the co-crystallized ligand present in the 5TZ1 structure. Molecular docking calculations were performed using AutoDock Vina with an exhaustiveness value of 100 to ensure an extensive conformational search of the active site.

2.2.3. Docking grid definition and docking protocol

The co-crystallized ligand was extracted from the protein structure and used to identify the active-site region of *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1). Molecular docking calculations were performed using AutoDock Vina. The docking grid was centered on the active-site cavity of the enzyme with grid center coordinates set to **x = 24.0, y = 22.0, and z = 24.0**. The dimensions of the docking box were defined as **22 × 22 × 22 Å**, ensuring complete coverage of the ligand-binding region. To improve the reliability of conformational sampling, the exhaustiveness parameter was set to **100**, while the number of output binding modes was fixed at **9**. The resulting ligand conformations were ranked according to their predicted binding affinities (kcal/mol), and the best-scoring poses were selected for further interaction analysis and visualization.

2.2.4. Docking validation

To validate the docking protocol, the co-crystallized ligand was redocked into the active site of DNA gyrase B. The superimposition of the crystallographic and redocked poses was analyzed using PyMOL, showing excellent agreement between the two conformations with an RMSD

value below 2.0 Å, thereby confirming the reliability and reproducibility of the docking procedure. Redocking of the co-crystallized ligand and RMSD analysis are commonly used to evaluate whether a docking protocol can reproduce the experimentally observed binding pose

2.2.5. Interaction analysis and methodological limitations

Protein–ligand interactions and binding conformations were analyzed and visualized using Discovery Studio 2021 Client and PyMOL. Therefore, the obtained docking scores primarily reflect ligand–protein interactions within the selected binding pocket and should be interpreted as preliminary estimates of binding potential rather than definitive evidence of inhibitory activity

3. RESULTS AND DISCUSSION

3.1. Antifungal activity

It was found that hydrazine (I) has a similarly high inhibitory effect against yeasts of the genus *Candida* (Table). Hydrazine (II) showed maximum antifungal activity against *C. albicans*, and its activity was 1.3 and 1.5 times higher than that against *C. guilliermondii* and *C. tropicalis*, respectively. Hydrazine III, IV, V and VI showed maximum activity against *C. albicans*, and this activity was 1.3–2.0 and 1.4–2.0 times higher than that against *C. guilliermondii* and *C. tropicalis*, respectively. It should be noted that *C. albicans* showed high sensitivity to all the studied substances and was 1.1–1.4 times higher than that against the antibiotic fluconazole. *C. guilliermondii* and *C. tropicalis* fungi showed high sensitivity to substances I and II, and low sensitivity to substances III – VI. In any case, the studied yeast species had high sensitivity to substance I, and their sensitivity was 1.4, 1.3 and 1.2 times higher than the sensitivity to the antibiotic fluconazole, respectively.

Table. Antifungal activity of hydrazine derivatives

Test Cultures	Compounds and diameter of inhibition zone (mm), M±m						
	I	II	III	IV	V	VI	Fluconazole
<i>Candida albicans</i>	26.3±1.0	25.3±1.2	26.0±1.2	20.0±0.9	26.0±1.2	20.0±0.8	18.0±0.8
<i>Candida guilliermondii</i>	26.0±0.9	20.0±0.9	14.0±0.6	14.0±0.7	13.0±0.4	13.4±0.4	20.0±0.6
<i>Candida tropicalis</i>	27.0±0.6	17.0±0.7	14.0±0.5	14.0±0.6	13.0±0.5	13.0±0.5	22.0±1.0

- I. (E)-1-(4-methoxybenzylidene)-2-phenylhydrazine
- II. (E)-1-(4-chlorobenzylidene)-2-(4-methoxyphenyl)hydrazine
- III. (E)-1-(4-nitrobenzylidene)-2-phenylhydrazine
- IV. (E)-1-(4-chlorobenzylidene)-2-(4-nitrophenyl)hydrazine
- V. (E)-1-(4-chlorobenzylidene)-2-phenylhydrazine
- VI. (E)-1-(4-chlorobenzylidene)-2-(p-tolyl)hydrazine

3.2. Molecular Docking Analysis of Compound 1, 2 and 6 against Lanosterol 14 α -Demethylase (5TZ1)

Compound 1 exhibited the highest binding affinity among the investigated derivatives, with a docking score of –4.7 kcal/mol. Analysis of the binding mode revealed the formation of a hydrogen bond between the hydrazone nitrogen atom and LYS358, while additional π -alkyl and

π -anion interactions were established with LEU340 and GLU336, respectively. The presence of multiple stabilizing contacts suggests that the hydrazone linker and aromatic fragments contribute significantly to ligand recognition within the CYP51 active site.

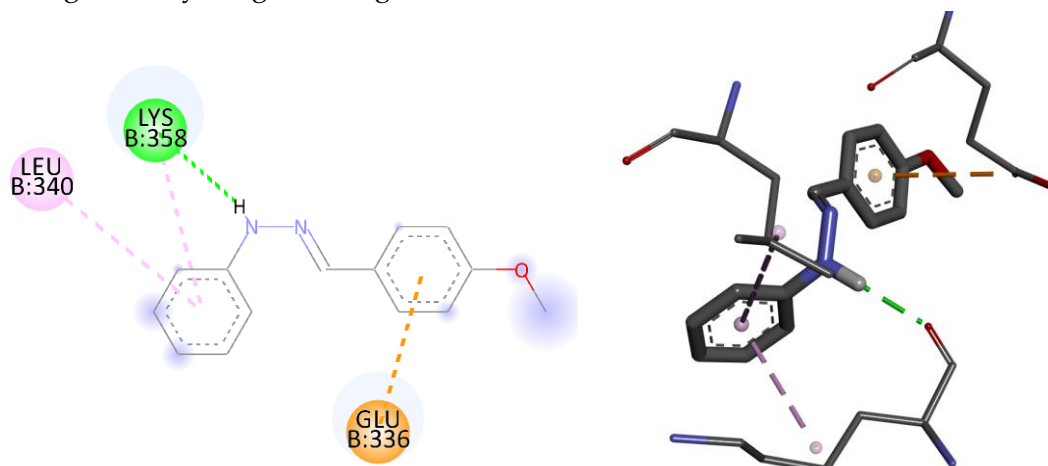


Figure 1. Docking interaction profile of Compound 1 with *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1): (A) 2D interaction map highlighting key amino acid residues involved in ligand binding; (B) 3D representation of the binding mode within the active site.

Compound 2 showed a binding affinity of -4.5 kcal/mol and interacted primarily with residues LYS358, LEU340, GLU336, GLU339, and GLU343. Compared with Compound 1, a larger number of amino acid residues participated in ligand stabilization, although the calculated binding affinity was slightly lower. The interaction pattern indicates that both aromatic rings contribute to the accommodation of the ligand within the binding cavity.

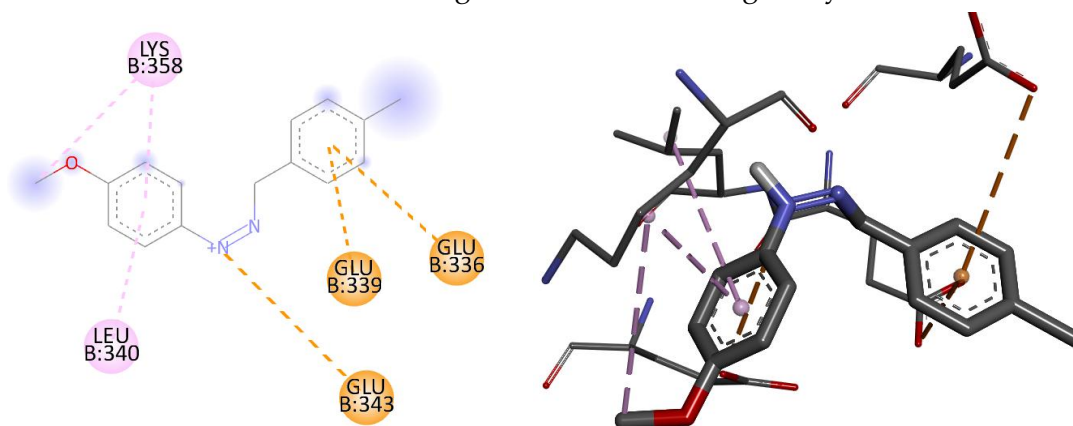


Figure 2. Docking interaction profile of Compound 2 with *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1): (A) 2D interaction map showing the principal ligand–residue contacts; (B) 3D visualization of the docked conformation in the enzyme binding pocket.

Compound 6 displayed a docking orientation characterized by a conventional hydrogen bond with LYS358 together with hydrophobic interactions involving LEU340 and π -mediated contacts with GLU336 and GLU343. The interaction profile was similar to that observed for Compound 1, highlighting the importance of the hydrazone scaffold in maintaining favorable contacts within the active site of lanosterol 14 α -demethylase.

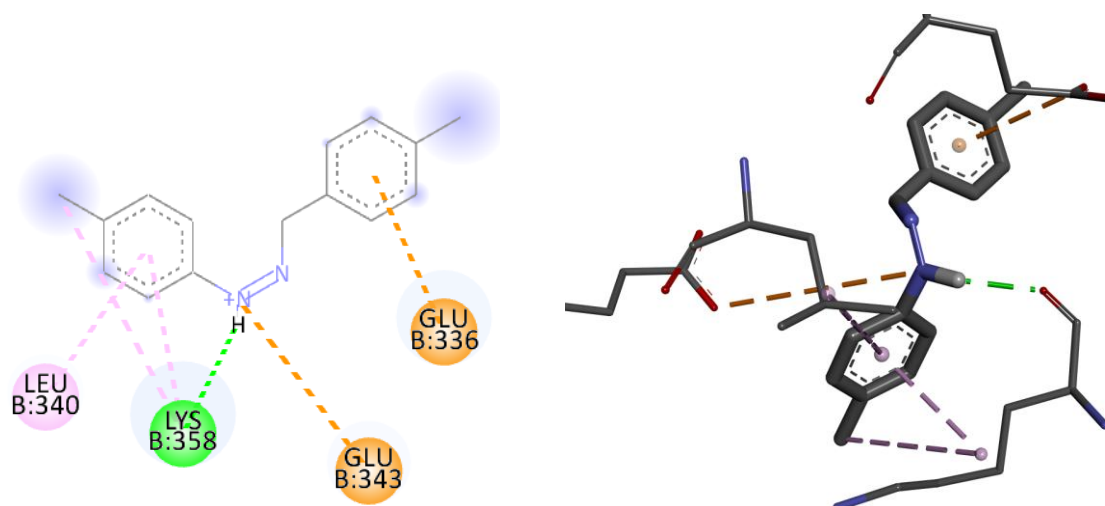


Figure 3. Docking interaction profile of Compound 6 with *Candida albicans* lanosterol 14 α -demethylase (CYP51, PDB ID: 5TZ1): (A) 2D interaction diagram illustrating the main non-covalent interactions; (B) 3D binding mode of the ligand within the active site of CYP51.

3.3. Comparative Analysis of Docking Results

Comparative analysis of the docking results revealed that all investigated hydrazone derivatives occupied a similar region within the active site of lanosterol 14 α -demethylase (CYP51). In all cases, LYS358 appeared as the most important residue, participating either in hydrogen-bond formation or hydrophobic stabilization. LEU340 was also frequently involved in ligand recognition through π -alkyl interactions. Furthermore, acidic residues such as GLU336, GLU339, and GLU343 contributed to ligand stabilization through π -type interactions.

Among the investigated compounds, Compound 1 exhibited the most favorable binding affinity (−4.7 kcal/mol), whereas Compounds 2 and 6 showed slightly lower docking scores. Despite these differences, the interaction profiles of all derivatives indicate that the hydrazone linkage and aromatic substituents play a crucial role in molecular recognition within the CYP51 binding cavity. The relatively similar docking energies suggest that structural modifications mainly affect the interaction pattern rather than the overall binding mode.

Although the docking scores were lower than that reported for the co-crystallized inhibitor oteseconazole, the ability of the synthesized compounds to establish multiple stabilizing interactions with key active-site residues supports their potential as antifungal candidates. These findings provide a theoretical basis for further biological evaluation and molecular dynamics investigations.

hydrophobic, and π -mediated interactions within the enzyme binding pocket. Among the docked compounds, Compound 1 exhibited the most favorable binding affinity, while Compounds 2 and 6 also demonstrated comparable interaction profiles.

Overall, the combined biological and computational findings suggest that hydrazone derivatives represent promising candidates for the development of new antifungal agents. The observed antifungal activity, together with their ability to interact with a biologically relevant fungal target, supports further optimization and in-depth investigations, including molecular dynamics simulations and in vivo studies.

4. CONCLUSION

In this study, a series of hydrazone derivatives were evaluated for their antifungal potential against *Candida* species and their interactions with *Candida albicans* lanosterol 14 α -demethylase (CYP51) were investigated using molecular docking analysis. The biological results demonstrated that the synthesized compounds exhibited varying degrees of antifungal activity against the tested fungal strains. Among them, **(E)-1-(4-methoxybenzylidene)-2-phenylhydrazine** showed the highest antifungal activity against all tested *Candida* species, displaying inhibitory effects that were 1.2–1.4 times greater than those of fluconazole.

Molecular docking studies revealed that the investigated compounds were able to occupy the active site of CYP51 and establish stabilizing interactions with key amino acid residues, including LYS358, LEU340, GLU336, GLU339, and GLU343. The docking results indicated that the hydrazone scaffold plays an important role in ligand recognition through hydrogen-bonding, hydrophobic, and π -mediated interactions within the enzyme binding pocket. Among the docked compounds, Compound 1 exhibited the most favorable binding affinity, while Compounds 2 and 6 also demonstrated comparable interaction profiles.

Overall, the combined biological and computational findings suggest that hydrazone derivatives represent promising candidates for the development of new antifungal agents. The observed antifungal activity, together with their ability to interact with a biologically relevant fungal target, supports further optimization and in-depth investigations, including molecular dynamics simulations and in vivo studies.

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ESTER-BASED CATIONIC GEMINI SURFACTANTS: SYNTHESIS, PROPERTIES, AND APPLICATIONS

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ARTICLE INFO	ABSTRACT
Article history: Received:2025-08-12 Received in revised form:2025-09-29 Accepted:2025-12-01 Available online: 2026-06-26 Keywords: Gemini surfactants; Cationic surfactants; Ester linkage; Biodegradability; Surface activity	Ester-based cationic gemini surfactants represent an innovative class of biodegradable amphiphiles that combine the exceptional surface-active properties of gemini structures with enhanced environmental compatibility. This comprehensive review examines the synthesis methodologies, physicochemical properties, and diverse applications of these surfactants, with particular emphasis on recent developments in the field. The incorporation of hydrolyzable ester linkages within the spacer or hydrophobic tails provides unique advantages, including controlled biodegradability, reduced toxicity, and maintained high surface activity. Critical micelle concentration values typically range from 0.01-0.1 mM, significantly lower than conventional monomeric surfactants. Recent studies demonstrate their effectiveness in biomedical applications, including gene delivery systems with transfection efficiencies comparable to commercial standards, antimicrobial agents with minimum inhibitory concentrations in the low micromolar range, and drug delivery vehicles. Additionally, these surfactants show promise in enhanced oil recovery, personal care formulations, and environmental remediation. Current challenges include synthetic complexity and industrial scaling limitations, while future perspectives focus on green synthesis methodologies, computational design approaches, and stimuli-responsive systems. This review highlights how ester-based cationic gemini surfactants successfully balance high performance with environmental responsibility, positioning them as next-generation surfactants for sustainable applications.

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1. INTRODUCTION

Surfactants constitute a fundamental class of chemical compounds with widespread applications across pharmaceutical, cosmetic, industrial, and environmental sectors. Traditional monomeric surfactants have served industry well for decades; however, their limited efficiency and environmental persistence have prompted researchers to develop more advanced alternatives [1]. Gemini surfactants, characterized by two hydrophilic head groups and two hydrophobic tails connected through a spacer unit, emerged as a revolutionary class of amphiphiles in the late 1990s, offering superior physicochemical properties compared to conventional surfactants [2].

The distinctive architecture of gemini surfactants confers remarkable advantages, including critical micelle concentration (CMC) values that are one to two orders of magnitude lower than

their monomeric counterparts, enhanced surface tension reduction capabilities, and superior solubilization properties [3]. These exceptional characteristics arise from the cooperative effects between the twin hydrophobic chains and the structural constraints imposed by the spacer unit. Among various types of gemini surfactants, cationic variants have attracted particular attention due to their strong electrostatic interactions with negatively charged surfaces, leading to enhanced antimicrobial properties and broad applicability in gene delivery systems [4].

Environmental sustainability has become an increasingly critical consideration in surfactant development. Conventional quaternary ammonium surfactants, while highly effective, exhibit poor biodegradability and

potential aquatic toxicity, raising concerns about their long-term environmental impact [5]. This challenge has driven the development of cleavable surfactants containing labile bonds that facilitate environmental degradation. Ester-based cationic gemini surfactants, featuring hydrolyzable ester linkages strategically positioned within their molecular architecture, represent a sophisticated solution that successfully balances high performance with environmental responsibility [6]. Recent research has demonstrated that these surfactants can achieve biodegradation efficiencies significantly superior to conventional cationic surfactants while maintaining excellent surface-active properties [7].

2. STRUCTURAL CLASSIFICATION AND DESIGN PRINCIPLES

Ester-based cationic gemini surfactants can be systematically classified according to the position and number of ester functionalities within their molecular structure. The general molecular formula comprises two quaternary ammonium head groups, two hydrophobic alkyl chains, and a spacer unit containing at least one ester bond ($-\text{COO}-$). The strategic positioning of ester linkages significantly influences both the physicochemical properties and biodegradation characteristics of these surfactants [8].

Spacer-integrated ester linkages represent the most common configuration, where ester bonds are incorporated within the spacer connecting the two hydrophilic head groups. This architecture facilitates controlled biodegradation while influencing the rigidity and flexibility of the spacer, thereby affecting micellization behavior and interfacial properties. Studies have shown that spacer-integrated esters generally result in higher CMC values compared to tail-integrated variants due to increased hydrophilicity of the spacer region [9]. Tail-integrated ester linkages, alternatively, feature ester bonds within the hydrophobic tails, often positioned between alkyl chains of varying lengths. This configuration enhances biodegradability while introducing polar interruptions that influence packing parameters and aggregation behaviors [10].

Recent advances have led to the development of multiple ester-functionalized gemini surfactants incorporating ester linkages in both spacer and tail regions. These sophisticated structures maximize biodegradability potential while offering complex self-assembly behaviors suitable for specialized applications. The cationic character typically derives from quaternary ammonium groups, which provide strong electrostatic interactions with negatively charged surfaces, contributing to enhanced surface activity and antimicrobial potency [11]. The combination of structural elements—hydrophobic chain length (typically C12-C18), spacer length (ranging from 2 to 12 carbon atoms), and ester positioning—enables fine-tuning of properties for specific application requirements.

3. SYNTHESIS METHODOLOGIES

The synthesis of ester-based cationic gemini surfactants typically involves multistep procedures requiring careful control of reaction conditions to achieve high yields and purity. Several established synthetic routes have been developed, each offering distinct advantages for specific molecular architectures [12]. The direct esterification route involves the reaction of dicarboxylic acids or their derivatives with long-chain alcohols containing tertiary amine functionalities. The resulting intermediates undergo quaternization with alkyl halides to yield the target gemini surfactants. This approach typically proceeds under acidic catalysis using *p*-toluenesulfonic acid or sulfuric acid, or through activation with coupling agents such as dicyclohexylcarbodiimide. Recent optimization studies have achieved yields exceeding 94% under carefully controlled conditions [13].

Transesterification methods provide an alternative approach involving reactions between methyl or ethyl esters of carboxylic acids and hydroxyl-functionalized quaternary ammonium compounds. This methodology often employs titanium(IV) alkoxides or sodium methoxide as catalysts, requiring careful control of temperature and pressure to drive the equilibrium toward product formation [14]. For surfactants with specific structural features, ring-opening reactions of cyclic anhydrides or lactones with amino-functionalized precursors offer an efficient strategy. The resulting intermediates undergo further functionalization and quaternization to yield target gemini structures with well-defined architectures [15].

Modern synthetic strategies have incorporated click chemistry principles, particularly copper(I)-catalyzed azide-alkyne cycloaddition, to construct ester-based gemini surfactants with precise control over structural elements. This modular approach allows for systematic variation of molecular parameters and facilitates structure-property relationship studies. Recent developments in green chemistry have focused on biocatalytic approaches using lipases for esterification, representing promising directions for environmentally benign synthesis while maintaining high selectivity and efficiency [16].

4. PHYSICOCHEMICAL PROPERTIES

Ester-based cationic gemini surfactants exhibit exceptional surface-active properties that significantly outperform conventional monomeric surfactants. The critical micelle concentration values typically range from 0.01 to 0.1 mM for surfactants with C12-C16 alkyl chains, compared to 1-10 mM for conventional monomeric surfactants with similar hydrophobic chain lengths. This enhanced efficiency stems from cooperative hydrophobic interactions between the two alkyl chains and structural constraints imposed by the spacer [17]. Recent studies have demonstrated that the position of ester linkages significantly influences CMC values, with spacer-integrated esters generally resulting in higher CMC compared to tail-integrated variants due to increased hydrophilicity of the spacer region [18].

Surface tension reduction capabilities represent another distinctive feature of these surfactants. They achieve significant reductions in the surface tension of water, typically reaching values of 25-30 mN/m at concentrations above the CMC, compared to 30-40 mN/m for conventional surfactants. The minimum surface tension depends on molecular architecture, with longer hydrophobic chains and optimized spacer lengths yielding lower values. Furthermore, these surfactants demonstrate remarkable interfacial activity, reducing oil-water interfacial tension to ultra-low values suitable for enhanced oil recovery applications [19].

The aggregation behavior reveals complex dependencies on molecular structure. Depending on spacer length, rigidity, and ester positioning, these surfactants form various micellar structures including spherical micelles, elongated or wormlike micelles, and vesicles. Short spacers (2-4 carbon atoms) typically promote formation of elongated structures due to strong repulsive interactions between headgroups, while longer spacers (10-12 carbon atoms) favor spherical aggregates. The average aggregation number typically ranges from 20 to 100, with ester linkages generally reducing aggregation numbers compared to all-hydrocarbon analogues due to increased hydrophilicity and steric constraints [20]. Recent research published in 2025 has shown that the presence of additional cationic groups significantly influences both CMC and aggregation behavior, with trimeric surfactants showing remarkable CMC reductions to 0.013 mM [21].

5. BIODEGRADABILITY AND ENVIRONMENTAL PROFILE

The defining feature of ester-based cationic gemini surfactants lies in their enhanced biodegradability compared to conventional quaternary ammonium surfactants. Ester bonds are susceptible to hydrolysis under both acidic and basic conditions, providing a mechanism for surfactant breakdown. The hydrolysis kinetics depend on several factors, including pH, temperature, and the steric environment surrounding the ester linkage. Generally, ester hydrolysis proceeds faster at extreme pH values and elevated temperatures. In neutral aqueous environments at ambient temperature, the hydrolytic half-life typically ranges from several days to weeks, providing a balance between stability during application and eventual degradability [22].

Microbial degradation proceeds primarily through enzymatic hydrolysis of ester bonds by esterases, generating fragments that can be further metabolized through conventional biodegradation pathways. Systematic investigations have established structure-biodegradability relationships, revealing that shorter spacers generally facilitate faster biodegradation due to reduced steric hindrance around ester groups, multiple ester functionalities enhance overall biodegradability, and branched alkyl chains near ester linkages can impede enzymatic hydrolysis [23]. Studies have demonstrated that spacer-integrated esters generally show faster biodegradation rates compared to tail-integrated esters due to greater accessibility to microbial enzymes.

A critical finding from recent research indicates that gemini surfactants with ester bonds are much more susceptible to alkaline hydrolysis than corresponding monomeric surfactants, particularly above the CMC. The betaine ester type arrangement, where the ester carbonyl group faces the positive charge, hydrolyzes significantly faster than esterquat surfactants. This differential hydrolysis behavior has important practical implications for formulation stability and environmental fate [24].

6. APPLICATIONS

The exceptional combination of high surface activity and enhanced biodegradability makes ester-based cationic gemini surfactants particularly valuable across diverse application domains. In biomedical applications, these surfactants have emerged as promising non-viral vectors for gene delivery. The positive charges of quaternary ammonium headgroups interact with negatively charged DNA phosphate backbone, forming compacted complexes (lipoplexes) that

facilitate cellular uptake. Recent studies published in 2024 have demonstrated transfection efficiencies comparable to commercial standards such as Lipofectamine, with the added advantage of significantly reduced cytotoxicity due to biodegradable ester linkages [25]. Structure-activity relationship investigations reveal that optimized spacer lengths (typically 3-6 carbon atoms) and balanced hydrophobic chain lengths (C12-C16) yield the most effective gene delivery systems.

Antimicrobial applications represent another significant domain. The intrinsic antimicrobial properties of quaternary ammonium compounds are enhanced in gemini structures through more efficient disruption of microbial cell membranes. Recent 2025 research has demonstrated broad-spectrum antimicrobial activity against both Gram-positive and Gram-negative bacteria, with minimum inhibitory concentrations often in the low micromolar range. Studies comparing these surfactants with known antimicrobials such as kanamycin and ampicillin have shown excellent activity in both *Staphylococcus aureus* and *Escherichia coli* [26]. The incorporation of ester linkages provides controlled degradation, potentially reducing antimicrobial resistance development.

In enhanced oil recovery applications, these surfactants reduce oil-water interfacial tension to ultra-low values, facilitating mobilization of residual oil trapped in reservoir pores. The cationic nature provides strong adsorption to negatively charged rock surfaces, modifying wettability toward more water-wet conditions that favor oil displacement. Recent 2024 studies have highlighted their effectiveness as fabric softening agents and corrosion inhibitors, with some gemini ester surfactants achieving corrosion inhibition efficiencies as high as 94.5% for carbon steel in acidic solutions [27]. Personal care applications benefit from their excellent conditioning properties, emulsion stabilization capabilities, and rheology modification effects at low concentrations.

7. CURRENT CHALLENGES AND FUTURE PERSPECTIVES

Despite significant advances, several challenges remain in the development and application of ester-based cationic gemini surfactants. Current synthetic routes often involve multiple steps with extensive purification requirements, limiting large-scale production feasibility. Overall yields in multistep syntheses of complex ester-based structures remain suboptimal, typically ranging from 30-60%. The development of more efficient one-pot synthesis methods and continuous flow processes represents a key challenge for industrial applications [28]. Furthermore, comprehensive understanding of structure-property relationships remains incomplete, necessitating advanced molecular dynamics simulations and quantum chemical calculations to predict the impact of ester positioning on aggregation behavior and interfacial properties.

Future research directions should focus on green chemistry approaches, emphasizing reduced solvent usage, non-toxic catalysts, and atom-economic transformations. Emerging biocatalytic approaches using lipases for esterification represent promising directions for environmentally benign synthesis. The development of stimuli-responsive systems with responsive behavior to specific stimuli (pH, temperature, light, enzymes) offers opportunities for smart delivery systems and controlled-release applications. Integration of ester-based cationic gemini architectures with other functional moieties, such as amino acids, sugars, or biodegradable polymers, represents an emerging approach to create multifunctional surfactants with enhanced performance profiles

[29]. The exploration of these surfactants in sustainable technologies, including biobased formulations and circular economy approaches, aligns with global sustainability goals and represents significant opportunities for future research.

8. CONCLUSION

Ester-based cationic gemini surfactants represent a sophisticated class of amphiphilic compounds that successfully address the balance between high performance and environmental responsibility. The strategic incorporation of biodegradable ester linkages within the molecular architecture delivers enhanced biodegradability while preserving exceptional surface-active properties characteristic of gemini structures. Their remarkably low CMC values (0.01-0.1 mM), superior surface tension reduction capabilities (25-30 mN/m), and versatile self-assembly behaviors position them as high-efficiency alternatives to conventional surfactants across diverse application domains. Recent research from 2024-2025 has demonstrated their significant potential in biomedical applications, including gene delivery systems with transfection efficiencies comparable to commercial standards, antimicrobial agents with excellent activity against both Gram-positive and Gram-negative bacteria, and corrosion inhibitors with efficiencies exceeding 94%. As sustainability considerations increasingly shape material selection across industries, these biodegradable surfactant architectures are poised to gain further importance, representing a significant opportunity to advance surfactant technology while aligning with global sustainability objectives and regulatory trends toward more environmentally responsible chemical solutions.

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AUTHOR GUIDELINES

1. Aims and Scope

Journal of Baku Engineering University – Advances in Chemistry and Chemical Engineering is an international, scholarly, peer-reviewed journal published twice a year, in print and online, by Baku Engineering University, Azerbaijan (P-ISSN 3134-6081; E-ISSN 3134-8866). It provides an international medium for original theoretical and experimental studies and reviews across chemistry and chemical engineering.

The scope of the Journal includes, but is not limited to: coordination chemistry; organometallic chemistry; general organic and bioorganic chemistry; chemical thermodynamics; instrumental analysis; natural and synthetic polymer chemistry; radiation chemistry; biochemistry; fermentation and bioengineering; food chemistry; environmental chemistry; green chemistry; inorganic chemistry; medicinal chemistry; petroleum chemistry and catalysis; photochemistry; surface chemistry; and chemical engineering and industrial chemistry.

2. Submission

The Journal accepts original, unpublished articles and reviews within the author's research field. Submissions are accepted only through the Journal's online submission system: <https://acce.beu.edu.az/>. Manuscripts sent by any other means are not considered. For correspondence, authors may write to acce@beu.edu.az.

No Article Processing Charge (APC) or any other fee is required for publication. All publication expenses are fully covered by Baku Engineering University.

3. Peer Review

Each submission is evaluated through double-blind peer review. The decision to publish is made through the following stages:

- The manuscript is sent to at least two independent experts.
- Based on the referees' recommendations, the manuscript is returned to the author for revision.
- After the author addresses the referees' comments, the Editorial Board makes the final decision on publication.

4. Manuscript Preparation

4.1 Language

Only English-language manuscripts are accepted.

4.2 Manuscript Length

The Journal accepts manuscripts in short format (7–10 pages) and long format (up to 25 pages). Manuscripts exceeding this limit should present a convincing justification.

4.3 File Format and Template

Please upload Word files (.doc or .docx), not PDF. Authors are encouraged to use the Journal's manuscript template: https://acce.beu.edu.az/acce_manuscript_template.zip.

4.4 Manuscript Structure

Manuscripts should include a title page, an introduction, the main text, and a conclusion. The title page should contain:

- Title of the manuscript
- Authors and affiliations
- Abstract (100–200 words)
- Keywords (5–7 single words or phrases)

The Introduction should start on a new page. There is no fixed structure for the main text.

4.5 Headings

First-level headings are in bold capitals — e.g., **3. MATERIALS AND METHODS**.

Second-level headings are in bold italics — e.g., ***3.1. Synthesis Procedure***.

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Figures, pictures, graphics and tables must be of publishing quality and placed within the text. Figures and graphics should be captioned beneath; tables should be captioned above.

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Atkins, P., de Paula, J., & Keeler, J. (2018). *Atkins' physical chemistry* (11th ed.). Oxford University Press.

Book chapter. Author, A. A., & Author, B. B. (Year). Title of the chapter. In *Title of the book* (pages). Publisher.

Hu, J., Chen, L., & Richards, R. (2009). Properties, synthesis and applications of highly dispersed metal oxide catalysts. In S. D. Jackson & J. S. J. Hargreaves (Eds.), *Metal Oxide Catalysis* (pp. 613–663). Wiley-VCH.

Journal article. Author, A. A., Author, B. B., & Author, C. C. (Year). Title of the article. *Title of the Periodical*, volume(issue), pages.

Hasanov, E. E., Rahimov, R. A., Abdullayev, Y., & Ahmadova, G. A. (2023). Symmetric and dissymmetric pseudo-gemini amphiphiles based on propoxylated ethyl piperazine and fatty acids. *ChemistrySelect*, 8(48), e202303942.

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5. Publication Ethics

By submitting, authors confirm that the manuscript is original, has not been published elsewhere, and is not under consideration by another journal. All sources must be properly cited, and all submissions are screened for plagiarism. Any conflicts of interest and funding sources should be disclosed.

6. Contact

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