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# UNDECYLENIC ACID AND N,N-DIBUTYLUNDECENAMIDE AS EFFECTIVE ANTIBACTERIALS AGAINST ANTIBIOTIC-RESISTANT STRAINS

*Y. D. STARTSEVA✉, D. M. HODYNA, I. V. SEMENYUTA, O. P. TARASYUK, S. P. ROGALSKY, L. O. METELYTSIA*

*V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Kyiv;*
*✉e-mail: startseva1991@gmail.com*

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*Evaluation of undecylenic acid (UA) and its tertiary amide N,N-dibutylundecenamide (DBUA) activity in vitro against the standard and antibiotic-resistant Escherichia coli and Staphylococcus aureus strains was carried out. The antibacterial potential of the acid and its amide at 2.5 and 5.0 μM concentration both against gram-positive bacteria (S. aureus) and gram-negative (E. coli) cultures was confirmed by monitoring the diameter of the bacterial growth inhibition zones. The docking study identified methionine aminopeptidase (MAP) as the most energy-favorable potential biotarget associated with the drug resistance of E. coli and S. aureus with a binding energy in the range from -8.0 to -8.5 kcal/mol. The ligands complexation was due to the formation of hydrogen bonds with ASP108, HIS171, HIS178, GLU204, GLU235, HIS76, ASP104, GLU233, ASP93 and metal-acceptor interactions with $Co^{2+}$. Overall, the results indicated that UA and DBUA activity against antibiotic-resistant strains creates prospects for the development of new antibacterial formulations.*

*K e y w o r d s: undecylenic acid, tertiary amide, Escherichia coli, Staphylococcus aureus, molecular docking, methionine aminopeptidase.*

Fatty acids (FAs) are widely distributed natural compounds with a wide spectrum of biological activity. It is known that they affect the functional activity of human and animal immune cells [1, 2], as well as participate in the protection of marine plants from unwanted colonizers [2-4]. In recent decades, there has been growing interest in the use of FAs in medicine, agriculture, and food production [2, 5]. These compounds are known to demonstrate antifungal activity against filamentous and non-filamentous unicellular fungi [6-8] and have antiviral potential against enveloped viruses [9].

An important feature of FAs is their biodegradability and low toxicity [2]. Many FAs can be produced on a large scale from natural sources such as vegetable oils. All this makes these compounds extremely promising for various biotechnological applications, in particular, for the prevention and treatment of fungal infections, for the preservation of food and cosmetic products, for the control of fungal infections of plants, etc. [2, 9]. Although FAs are known for their antifungal activity, they have not yet found wide commercial use in the treatment of related infectious diseases in humans and animals.

One of the best-known antifungal fatty acids is UA, which is produced commercially by pyrolysis of ricinoleic acid from castor oil [10]. UA is widely used as an active ingredient in many topical antifungals for the treatment of surface infections [9-11]. Some UA derivatives, including morpholide [12], monoethanolamide [13], and monoglyceride [14], also have antifungal activity, although less than the UA. However, there is little data in the literature concerning the antibacterial activity of UA and its derivatives, especially against antibiotic-resistant clinical isolates. Recent studies have shown that both UA and its derivatives can be effective modifiers for engineering thermoplastics. Thus, the preparation of antifungal poly(methyl methacrylate) based material (PMMA/UA) has been reported in [15]. The composite containing 6% UA reduced the cellular Candida biocenosis by more than 90%. Tertiary amide of UA, namely DBUA was found to be a new eco-friendly plasticizer for polyvinyl chloride (PVC),

alternative to commonly used toxic phthalate esters [16]. Overall, the results of our preliminary studies indicate that DBUA has much better compatibility with engineering thermoplastics in comparison with UA or its esters. Accordingly, it seems extremely promising bifunctional additive for various polymer articles and protective coatings. However, the antimicrobial activity of DBUA has not yet been studied.

The study of the mechanism of action of antibacterial agents of various structures is of special interest. Such works aim the search and analysis of specific inhibitors that provide high efficiency against antibiotic-resistant strains. UA and DBUA are presented by the ChEMBL database as potential inhibitors of a number of enzymes including methionine aminopeptidases (MAP) [17], dihydrofolate reductase (DHFR) [18], alanyl aminopeptidase (AAPS) [19], and serine/threonine protein kinase (STPK) [20] associated with bacterial resistance. Methionine aminopeptidases (EC 3.4.11.18) belong to metalloenzymes that split the N-terminal methionine from synthesized proteins and peptides. Many authors indicate that MAP-1 ensures the bacteria's vital activity and can be successfully used as a biotarget for different antibacterials [21-23]. In this article, the antibacterial activity of UA and its tertiary amide (DBUA) has been studied against the standard and antibiotic-resistant *Escherichia coli* and *Staphylococcus aureus* strains. Moreover, the molecular docking of tested compounds in the active site of the known antibacterial target methionine aminopeptidase has been conducted.

## Materials and Methods

*Chemistry.* Following chemicals were used for the synthesis: undecylenic acid (98%), dibutylamine (99.5%), triethylamine (for synthesis), thionyl chloride (97%), chloroform (99%), dichloromethane (99.8%), hydrochloric acid (37%) (Sigma-Aldrich).

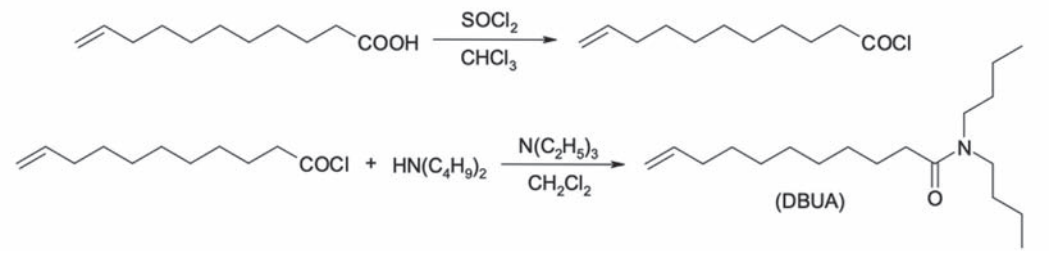
Tertiary amide DBUA was synthesized according to Scheme using the method described in [16]. The solution of undecylenic acid (20 g, 0.1 mol), thionyl chloride (11 ml, 0.15 mol) and 0.2 g of triethylamine in 150 ml of chloroform was heated to gentle boiling for 6 h. Chloroform was distilled off, and residual volatile products were removed under vacuum of 10 mbar at 50°C for 8 h. The crude undecenoyl chloride was prepared as brown liquid.

The solution of dibutylamine (12.9 g, 0.1 mol) and triethylamine (10 g, 0.1 mol) in 150 ml of dichloromethane was cooled in an ice bath. To this stirred mixture was added dropwise crude undecenoyl chloride. The reaction was carried out for 1 h at 0-5°C and 3 h at room temperature. The mixture was then washed with water (200 ml), diluted hydrochloric acid (5%, 2×100 ml) and water solution of 10% potassium hydroxide (200 ml). The solution of product in dichloromethane was dried over sodium sulfate. Dichloromethane was removed by distillation. The prepared low viscous liquid of light brown color was dried in vacuum 10 mbar at 70°C.

The structure of synthesized compound was confirmed by nuclear magnetic resonance (NMR) technique. $^1$H NMR spectrum was recorded in $CDCl_3$ on a Varian Gemini-2000 (400 MHz) spectrometer.

$^1$H NMR (400 MHz, $CDCl_3$) δ: 0.93 (t, 6H, $CH_3$), 1.3 (m, 14H, $(CH_2)_5$, $-NCH_2CH_2CH_2$), 1.49 (m, 4H, $NCH_2CH_2$), 1.63 (m, 2H, $-CH_2CH_2CO-$), 2.03 (m, 2H, $-CH_2=CH-CH_2-$), 2.28 (t, 2H, $-CH_2CO-$), 3.2 (t, 2H, $NCH_2$), 3.3 (t, 2H, $NCH_2$), 4.94 (m, 2H, $-CH_2=CH-$), 5.82 (m, 1H, $-CH_2=CH-$).

*Biology.* The antibacterial activity of UA and DBUA was evaluated *in vitro* both against standard strains *S. aureus* (ATCC 5923) and *E. coli* (ATCC 25922), as well as its clinical antibiotic-resistant isolates. All used bacterial cultures were received from the Museum of Microbial Culture Collection of the Shupyk National Healthcare University of Ukraine. Antibacterial properties were determined by the disc diffusion method in Mueller-Hinton agar [24]. A final inoculum concentration of $1 \cdot 10^5$ colony-forming




*Scheme. Synthesis of tertiary amide of undecylenic acid DBUA*

unit (CFU) per ml was established using a 0.5 McFarland turbidity standard. The subsequent dilution of 0.02 ml of the tested compounds was applied on standard paper disks (6 mm) which were placed on the agar plate. All tested compounds were dissolved in DMSO. Neat DMSO was used as a negative control.

Ampicillin (semi-synthetic penicillins), Ceftazidime (third-generation cephalosporins), and Cefoxitin (second-generation cephalosporins) were used as reference drugs with a wide spectrum of antibacterial activity. The mechanism of action of the applied antibiotics is associated with the synthesis inhibiting of the bacterial cell wall.

*Docking procedure.* The protein 3D structures of MAPs of *E. coli* (PDB ID:1C22) and *S. aureus* (PDB ID:1QXW), DHFRs *E. coli* (PDB ID:1RC4) and *S. aureus* (PDB ID:6P9Z), AAP *E. coli* (PDB ID: 2DQM) and aminopeptidase S (AAPS) *S. aureus* (PDB ID: 1ZJC), STPKs *E. coli* (PDB ID:4JX7) and *S. aureus* (PDB ID:4EQM) were imported from the RCSB Protein Data Bank. The proteins and ligands were made AutoDock Tools (ADT) 1.5.6 [25]. All hydrogen atoms were added to protein molecules using ADT, then the total atoms were renumbered. The Gasteiger method [26] was operated to calculate and add the partial charges and then protein molecules were saved in the PDBQT format. The ligand structures and conformations were created by ChemAxon Marvin Sketch 5.3.735 program (ChemAxon Marvin Sketch, 5.3.735. Available from: https://www.chemaxon.com/ (accessed on February 12, 2023)) and saved in the mol2 format. The optimization and the energy minimization of ligand structures were conducted by Avogadro v1.2.0 program. The AutoDock Vina 1.1.2 program was used in docking studies. The docking centers are the co-crystallized ligands in the protein structures. A grid step of 1.0 Å and a grid of 30×30×30 points were used. The analysis of the protein-ligand interactions and graphical representation of the calculated results were performed using Accelrys DS (Discovery Studio Visualizer, v4.0.100.13345. Available from: https://discover.3ds.com/ (accessed on February 12, 2023)).

## Results

The results presented in Table 1 indicate that UA and its derivative DBUA have a similar high antibacterial potential against both ATCC strains and clinical antibiotic-resistant clinical isolate strains. The established type of activity is dose-dependent and practically similar against both the gram-positive *S. aureus* strain and gram-negative *E. coli* strain. Thus, UA and DBUA with a content of 5.0 μmol on the disk formed the diameters of the bacterial growth inhibition zones with an average diameter of 36 mm for all studied strains. When the amount of the tested compounds was reduced to 2.5 μmol, the growth inhibition zones of both cultures decreased only by 1.4 times (Table 1).

At the same time, the reference antibiotics Ampicillin and Cefoxitin with a significantly reduced content on standard disks of 0.03 and 0.07 μmol, respectively, showed activity only against ATCC bacterial strains, while Ceftazidime (0.06 μmol on disk) was inactive against both ATCC bacterial strains and antibiotic-resistant clinical isolates (Table 1).

The positive *in vitro* results of the study of the antibacterial activity of UA and DBUA seem promising and allowed us to propose some hypotheses regarding the potential mechanism of its antibacterial action based on docking studies.

*Molecular docking.* Docking analysis of potential biotargets associated with the antibacterial activity of studied compounds against drug-resistant strains is presented in Table 2.

The formed ligand-protein complexes showed the calculated binding energy from -4.4 to - 8.5 kcal/mol (Table 2). The most energetically favorable ligand-protein complexation is observed in the interaction of ligands in the MAP *E. coli*/*S. aureus* active centers with a binding energy of -8.0 and -8.5 kcal/mol. The obtained *in silico* results allow us to propose activity of UA and DBUA is probably associated with the inhibiting of the MAP *E. coli* and *S. aureus.*

The docking of UA and DBUA was conducted in the active center of the *E. coli* MAP based on the binding energy calculated values. The localization of co-crystallized with MAP trifluoromethionine [27] was used as a docking center. Features of the complexation of studied ligands into the MAP substrate binding site are shown in Fig. 1.

The docking results indicate (Fig. 1) that the formation of the ligand-protein complexes of UA and DBUA into the *E. coli* enzyme active center occurs similarly with the calculated binding energy of -8.0 and -8.3 kcal/mol, respectively. The formed complexes are stabilized by hydrogen bonds (2.12–3.39 Å) with the amino acid residues ASP108, HIS171, HIS178, GLU204, GLU235, and metal-acceptor interactions (2.21–2.66 Å) with atoms $Co^{2+}$.

*Table 1. In vitro antibacterial activity (mm) of UA and DBUA, (M ± m, n = 3)*

| № | Compound name | Content on disk, μmol | *S. aureus* (ATCC 5923) | *S. aureus* (clinical isolate) | *E. coli* (ATCC 25922) | *E. coli* (clinical isolate) |
|---|---|---|---|---|---|---|
| 1 | UA | 5.0 | 39.3 ± 0.3 | 33.0 ± 0.6 | 38.0 ± 0.6 | 36.3 ± 0.3 |
| | | 2.5 | 31.7 ± 0.3 | 26.7 ± 0.6 | 30.6 ± 0.3 | 27.6 ± 0.3 |
| 2 | DBUA | 5.0 | 38.0 ± 0.6 | 30.7 ± 0.6 | 40.3 ± 0.3 | 37.3 ± 0.3 |
| | | 2.5 | 31.0 ± 0.6 | 27.0 ± 0.6 | 29.7 ± 0.3 | 30.7 ± 0.3 |
| 3 | Ampicillin | 0.03 | 30.7 ± 0.6 | na | 35.0 ± 0.6 | na |
| 4 | Ceftazidime | 0.06 | na | na | na | na |
| 5 | Cefoxitin | 0.07 | 36.3 ± 0.3 | na | 16.7 ± 0.3 | na |

Note. na – no activity

*Table 2. Comparative analysis of the calculated binding energy of the complexation UA and DBUA into the active site of E. coli/S. aureus potential molecular biotargets*

| Potential molecular biotargets | Binding energy (ΔG) of *E. coli*/*S. aureus* coplexation, kcal/mol | |
|---|---|---|
| | Undecylenic acid | N,N-dibutylundecenamide |
| Methionine aminopeptidase (MAP) | -8.0/-8.2 | -8.3/-8.5 |
| Dihydrofolate reductase (DHFR) | -4.8/-4.4 | -5.7/-4.9 |
| Alanyl aminopeptidase (AAP) *E. coli*<br>Aminopeptidase S (AAPS) *S. aureus* | -5.5/-5.0 | -5.8/-5.4 |
| Serine/threonine protein kinase (STPK) | -5.4/-5.2 | -5.9/-5.6 |

Fig. 2 demonstrates the features of interaction of UA and DBUA in the active center of *S. aureus* MAP. Thus, it indicates the formation of the protein-ligand complexes between these compounds and the *S. aureus* enzyme active center with the estimated binding energy of -8.2 and -8.5 kcal/mol. Also, the formed ligand-protein complexes were stabilized by hydrogen bonds (2.11–3.44 Å) with the amino acids HIS76, ASP104, GLU233, ASP93, and with metal-acceptor interactions (2.14–2.19 Å) with atoms $Co^{2+}$.

## Discussion

Natural compounds are essential components of the modern pharmaceutical base. However, the widespread use of these drugs has led to the rapid development of drug-resistant strains, which are the main cause of failure in various areas of their use.

From this point of view, UA and its derivatives seem to be important objects in the search and analysis of new biologically active agents. It is known that UA, like many other FAs, has a high fungicidal/fungistatic potential [28, 29]. It is effective against the fungi *Candida albicans*, both against its round yeast form and micelles form with elongated hyphae, the presence of which many authors associate with the virulence of the fungal pathogen [30, 31]. Many studies indicate that UA breaks the formation of *Candida albicans* biofilms by inhibiting the transcription level of HWP1 genes [8]. UA can also inhibit the enzymes involved in lipid metabolism and slows down the protons transmembrane transport, thereby changing the cytoplasm pH.

The other long-chain fatty acids, capric acid and lauric acid, inhibit the growth of planktonic *Candida* cells [32]. Stearidonic acid, eicosapentaenoic acid, docosapentaenoic acid [33], and conjugated linoleic acid inhibit the growth of *C. albicans* hyphae [34], trans-2-decenoic acid [35], undecenoic acid [36], and myristic acid [37] inhibit hyphal growth and biofilm formation. However, long-chain unsaturated FAs such as arachidonic acid, oleic acid, linolenic acid, or γ-linolenic acid did not affect the hyphae development [8]. More recently, oleic acid [38] and linoleic acid [32, 39] have been reported to inhibit filamentation and biofilm formation in *C. albicans* without affecting on planktonic cells growth.

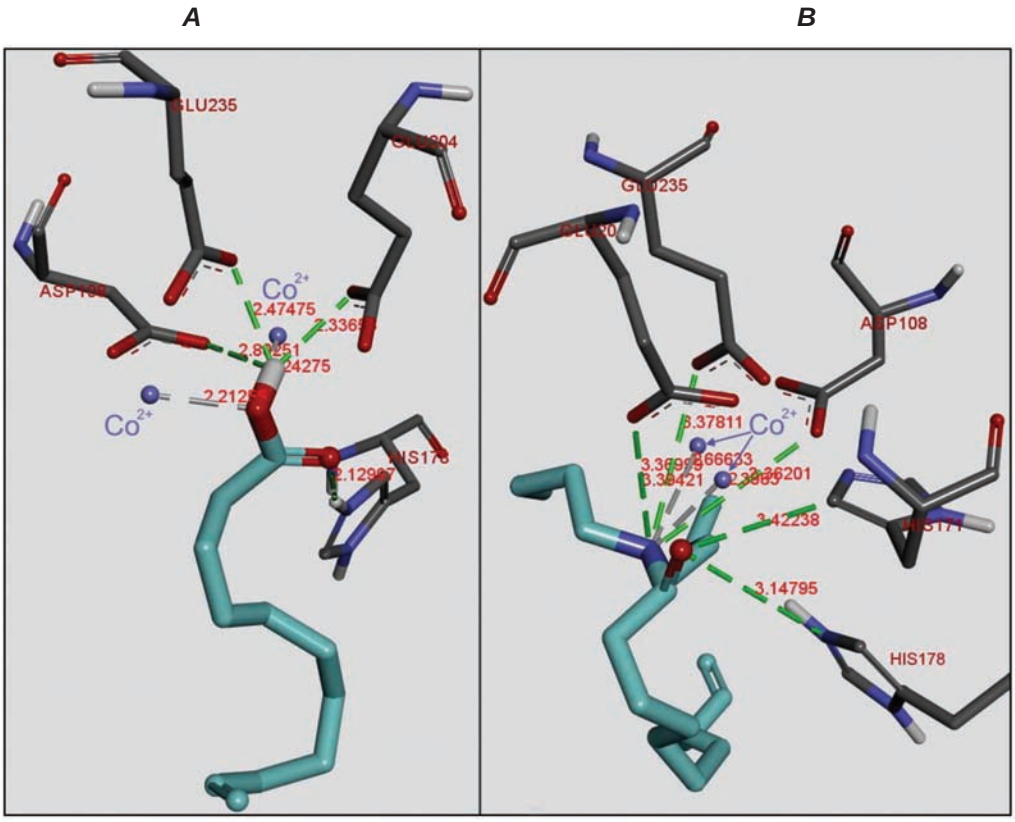



*Fig. 1. Docking the UA (**A**) and DBUA (**B**) into the substrate binding site of E. coli MAP; blue – ligands*

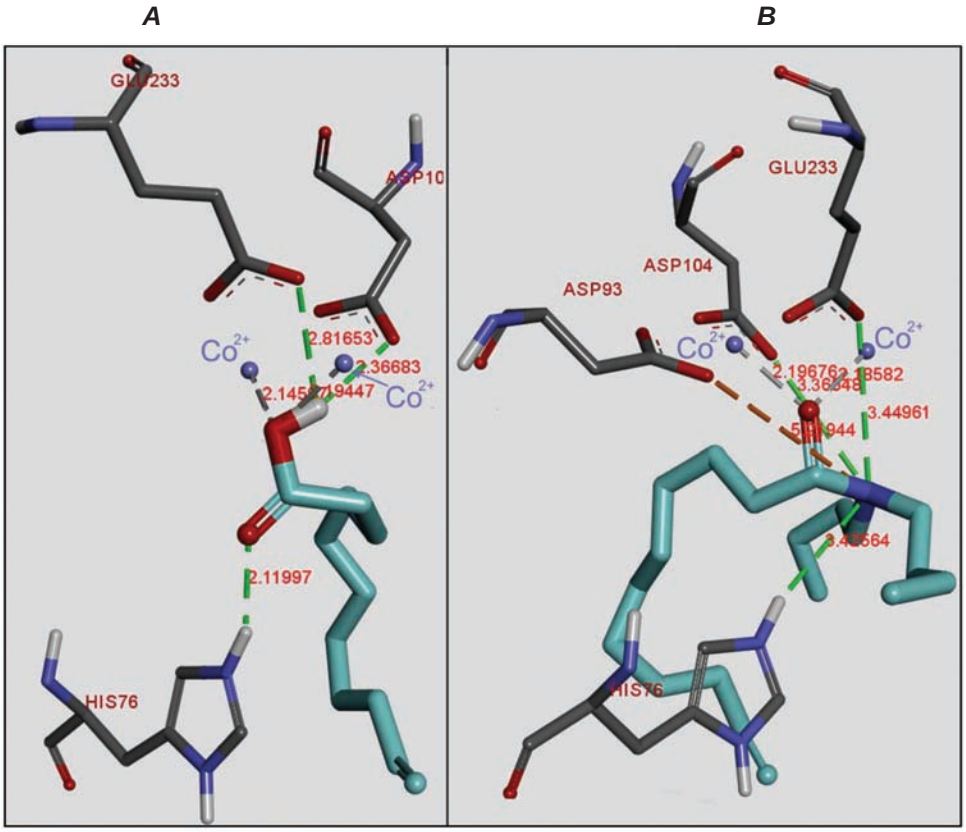



*Fig. 2. Docking the UA (**A**) and DBUA (**B**) into the substrate binding site of S. aureus MAP; blue – ligands*

Of particular interest are studies of FAs and their derivatives as antibacterial agents, especially against antibiotic-resistant bacterial pathogens. Importantly, these natural molecules do not cause microbial drug resistance. Since many microbial pathogens react differently to various natural and synthetic FAs, current research is focused on *in vitro* and *in silico* studies of the unique features of FAs and their derivatives, which certainly represent a new paradigm in the fight against resistant microbial pathogens.

Some FAs have antibacterial activity, but the level of their manifestation is quite low and limited. For example, antistaphylococcal activity has been reported for linoleic acid from the ascomycete Hypoxylon fragiforme [40]. There are literature data that lauric acid exhibits antibacterial activity against *Staphylococcus aureus* and *Streptococcus pneumoniae* with zones of inhibition up to 15 mm, and against *Mycobacterium tuberculosis*, *Escherichia coli* and *Salmonella spp.* with zones of bacterial growth inhibition around 8 mm [41]. Palmitic acid and stearic acid encapsulated in liposomal carriers exhibit bactericidal activity against *Staphylococcus epidermidis* and *Enterococcus faecalis* [42].

The obtained experimental results of UA and DBUA activity against the standard and antibiotic-resistant bacterial strains showed its high antibacterial potential. It was found by the disk diffusion method that the activity of UA and DBUA with content on the disk of 5 μmol is average 38.6 mm against *S. aureus* (ATCC 5923) strain and 31.3 mm against clinical isolate strain *S. aureus*, respectively. The activity of UA and DBUA with content on the disk of 2.5 μmol was authentically similar and amounted to 31.3 mm both against *S. aureus* (ATCC 5923) strain and clinical isolate *S. aureus.* The anti-*E. coli* activity of the UA and DBUA (with 5 μmol on the disk) was average 39.1 mm against both bacterial cultures. A decrease in the content of both compounds on the disk to 2.5 μmol led to a slight reduction in their activity and averaged 29.1 mm both against *E. coli* (ATCC 25922) and *E. coli* (clinical isolate). The obtained results agree with those of recent research, in which the antibacterial activity of tertiary fatty amide, N,N-dibutyloleamide (DBOA) against *E. coli* and *S. aureus* clinical isolates has also been found [43]. However, significantly lower inhibition zone diameters (around 15 mm) were determined for both bacterial strains, as compared with DBUA.

The calculated results obtained by the molecular docking method allowed us to suggest a potential molecular mechanism of the antibacterial action of the studied compounds against antibiotic-resistant strains. The analysis of the 4 potential antibacterial biotargets associated with microbial resistance including methionine aminopeptidase, dihydrofolate reductase, alanyl aminopeptidase, and serine/threonine protein kinase, allowed us to identify the methionine aminopeptidase as the most energy-favorable potential biotarget. The complexation of UA and DBUA in the *E. coli* and *S. aureus* MAP active centers was accompanied by the calculated binding energy (ΔG) from -8.0 to -8.5 kcal/mol. The formed complexes were stabilized by a series of hydrogen bonds with ASP108, HIS171, HIS178, GLU204, GLU235, HIS76, ASP104, GLU233, ASP93 amino acid residues and several metal-acceptor interactions with atoms $Co^{2+}$. Furthermore, the obtained comparable docking positions of the ligands and high calculated binding energies in the range from -8.0 to -8.5 kcal/mol may indicate a correct and promising docking strategy used in the work.

*Conclusions.* The results of *in silico* and *in vitro* studies of UA and its tertiary amide DBUA revealed their high antibacterial potential. The antibacterial activity provided by 2.5 μmol/5.0 μmol of UA and DBUA against both standard and antibiotic-resistant clinical isolates is equally high. It is worth noting that both UA and its amide demonstrated activity against the gram-positive bacterial culture (*S. aureus*) and gram-negative culture (*E. coli*). This fact indicates the possibility of the spectrum expanding of pathogens as potential microbial targets for the analysis of new bioactive compounds with similar structural features. This is especially important for a group of gram-negative bacterial micropathogens, the cell wall of which, due to its more complex structure, is more resistant to antibacterials than the cell wall of gram-positive bacteria.

The study of the molecular mechanism of action features of the UA and DBUA by molecular docking allowed us speculate about potential antibacterial biotargets. MAP has been identified as the most energetically favorable potential biotarget associated with drug-resistant *E. coli* and *S. aureus* strains. The complex formation of UA and DBUA into the binding sites of the *E. coli* and *S. aureus* MAP substrate occurred with calculated binding energy from -8.0 to -8.5 kcal/mol. The ligand-protein complexes are stabilized by hydrogen bonds with

amino acids ASP108, HIS171, HIS178, GLU204, GLU235, HIS76, ASP104, GLU233, ASP93 and by metal acceptor interactions with $Co^{2+}$ atoms.

Overall, the results of this study confirmed broad prospects of UA and its tertiary amide DBUA for the development of new safe antibacterial formulations, especially for the treatment of drug-resistant human infections. However, further studies are needed for better understanding the mechanisms of antibacterial actions of these compounds, as well as their efficacy against clinically important microorganisms.

*Conflict of interest.* Authors have completed the Unified Conflicts of Interest form at http://ukrbiochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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## УНДЕЦЕНОВА КИСЛОТА ТА N,N-ДИБУТИЛУНДЕЦИЕНАМІД ЯК ЕФЕКТИВНИЙ АНТИБАКТЕРІАЛЬНИЙ ЗАСІБ ПРОТИ АНТИБІОТИКОСТІЙКИХ ШТАМІВ

*Ю. Д. Старцева*✉*, Д. М. Година, І. В. Семенюта, О. П. Тарасюк, С. П. Рогальський, Л. О. Метелиця*

*Інститут біоорганічної хімії та нафтохімії ім. В. П. Кухаря НАН України, Київ;*
✉*e-mail: startseva1991@gmail.com*

Проведено оцінку активності ундецилено-вої кислоти (УК) та її третинного аміду N,N-дибутилундеценаміду (ДБУК) *in vitro* проти стандартних та антибіотикорезистентних штамів *Escherichia coli* та *Staphylococcus aureus*. Антибактеріальний потенціал кислоти та її аміду в концентраціях 2,5 і 5,0 мкМ як проти грампозитивних бактеріальних (*S. aureus*), так і грамнегативних (*E. coli*) культур підтверджено моніторингом діаметра зон пригнічення росту бактерій. Докінг-дослідження визначило метіонінамінопептидазу (MAP) як найбільш енергетично сприятливу потенційну біомішень, асоційовану з лікарською стійкістю *E. coli* та *S. aureus* з енергією зв'язування в діапазоні від -8,0 до -8,5 ккал/моль. Комплексоутворення лігандів відбувалося за рахунок утворення водневих зв'язків з ASP108, HIS171, HIS178, GLU204, GLU235, HIS76, ASP104, GLU233, ASP93 та металоакцепторної взаємодії з $Co^{2+}$. Отримані результати показали, що активність UA та DBUA проти антибіотикорезистентних штамів створює перспективи для розробки нових антибактеріальних препаратів.

Ключові слова: ундеценова кислота, третинний амід, *Escherichia coli*, *Staphylococcus aureus*, молекулярний докінг, метіонінамінопептидаза.

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