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ANTIMICROBIAL AND ANTIFUNGAL ACTIVITIES OF SOME ANTHRACENEDIONE DERIVATIVES

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ABSTRACT

The aim of the work is to carry out the synthesis of a series of functionally substituted anthraquinone derivatives, to investigate their antimicrobial activity, and to predict the drug-likeness of the obtained compounds using modern web-based tools.

Materials and methods. Standard methods of organic synthesis were employed, and physicochemical characterization of the synthesized compounds was performed. The antimicrobial activity was evaluated using the agar diffusion method and the serial dilution method in accordance with generally accepted microbiological protocols. *In silico* drug-likeness screening of the synthesized compounds was carried out using the SwissADME online service.

Results and discussion. A series of new functionally substituted anthraquinone derivatives was synthesized. Based on the results of antimicrobial activity screening, compound 5 was identified as the hit compound, exhibiting the highest level of activity among the tested compounds. It was found that other anthracenedione derivatives do not exhibit pronounced antimicrobial and fungistatic activity, which may be due to the peculiarities of their chemical structure. The results obtained indicate the prospects for further research into anthracenedione derivatives as potential antimicrobial agents.

Conclusions. A series of four functionally substituted anthraquinone derivatives was synthesized and their antimicrobial activity was evaluated. Compound 5 was found to exhibit antimicrobial activity against Gram-positive microorganisms, whereas the other tested compounds showed no detectable activity under the same conditions. In silico prediction of drug-likeness and potential toxicity for compound 5 using modern web-based tools indicated favorable pharmacokinetic properties and no obvious signs of toxicity. These results highlight the potential of functionally substituted anthraquinone derivatives for further investigation as prospective antimicrobial agents.

Introduction. Against the backdrop of the rapid spread of antimicrobial resistance (AMR), which constitutes one of the most significant global threats to human health and calls into question the effectiveness of standard medical interventions and the treatment of infectious diseases, the primary task for the near and medium term becomes the search for and development of new chemical compounds with antimicrobial activity to overcome this crisis. According to estimates, in 2019, bacterial AMR directly caused 1.27 million deaths, and this figure could rise to 10 million fatalities annually by 2050, which underscores the urgent need for innovative antimicrobial agents [1–3].

Among various classes of biologically active compounds, anthracenedione (anthraquinone) derivatives have attracted considerable attention due to their broad spectrum of pharmacological properties, including antimicrobial, antifungal, antiviral, anti-inflammatory and anticancer activities [4; 5]. The biological potential of anthracenedione derivatives is largely determined by their planar aromatic structure and the presence of reactive carbonyl groups, which enable interactions with nucleic acids and a wide range of cellular enzymes. Anthraquinones exert their biological activity through DNA intercalation, inhibition of topoisomerases, redox cycling with reactive oxygen species generation, modulation of cellular enzymes – including tyrosinase – and induction of mitochondrial dysfunction and apoptosis [6–8]. In addition, this class of compounds has become an important subject of computational chemistry studies, including *in silico* prediction of biological activity, pharmacokinetic and toxicological profiling, molecular docking, and structure–activity relationship (SAR) analysis [9]. Beyond their pharmacological potential, anthracenedione derivatives are actively investigated in bioimaging, as their tunable photophysical properties make anthraquinones a versatile platform for developing novel luminophores with enhanced fluorescence properties and imaging agents for biological systems [10].

Structural modification of the anthracenedione core – in particular, the introduction of cyanoamine, hydroxyl, or halogen substituents – has been shown to enhance biological activity and improve selectivity toward different microbial strains [11–14]. These modifications can modulate lipophilicity, electronic distribution, and hydrogen-bonding capacity, thereby strengthening interactions with microbial targets such as DNA, cell wall enzymes, and critical metabolic proteins. As a result, anthracenedione derivatives can inhibit microbial replication, disrupt cell membrane integrity, interfere with enzymatic pathways, and induce oxidative stress, collectively contributing to potent antimicrobial and antifungal effects [9; 10]. Therefore, the rational design and synthesis of new anthracenedione derivatives represent a promising strategy for developing novel antimicrobial agents capable of overcoming multidrug resistance and addressing the growing global challenge of resistant infections.

Materials and methods. During the study, methods of organic synthesis were employed, and the synthesized compounds were physicochemically analysed using ^{1}H NMR spectroscopy and mass spectrometry.

To assess antimicrobial activity, the agar diffusion method was employed, utilizing a range of reference and clinical microbial strains. To assess antimicrobial activity, the agar diffusion method was employed using a panel of reference and clinical microbial strains. The tested microorganisms included Gram-positive bacteria: *Staphylococcus aureus* subsp. *aureus* ATCC 25923 (biofilm-positive), *Staphylococcus aureus* B2, *Staphylococcus epidermidis* ATCC 12228 (non-biofilm-forming), *Streptococcus agalactiae* ATCC 13813, and *Enterococcus* spp. (non-MDR, 2/4); Gram-negative bacteria: *Pseudomonas aeruginosa* ATCC 10145, *Klebsiella pneumoniae*, *Klebsiella variicola*, *Raoultella ornithinolytica* DSM 7464 (= ATCC 31898); yeast fungi: *Candida albicans* and *Candida albicans* 85; a mold fungus: *Aspergillus niger*; as well as a non-pathogenic lactic acid bacterium, *Lactobacillus fermentum*. The full list of strains is presented in Table 1. For this procedure, microbial cultures adjusted to a 0.5 McFarland standard were used to inoculate plates of either Muller-Hinton agar (M173, Himedia) or Sabouraud agar. Clean, sterile paper discs (Himedia Laboratories Pvt. Limited, India) were each loaded with 20 µl of the test compounds (at a concentration of 5 mg/ml) and then positioned on the surface of the inoculated agar. The diameter of the growth inhibition zone surrounding each disc was measured after 24–48 hours of incubation for bacteria. For the mold fungus, observations were extended for up to 14 days, with conidia maturation in *Aspergillus* also being recorded. It was noted that all biofilm-producing strains possessed the *pox* gene, which is associated with biofilm formation.

The solvent, dimethyl sulfoxide (DMSO), was permitted to air-dry completely before the discs were transferred onto nutrient agar plates (Biolife Italiana S.r.l.) containing a 3% erythromass supplement. A bacterial suspension equivalent to 0.5 McFarland turbidity was then applied. Pure DMSO was utilized as a control in these experiments. Incubation was carried out at 37°C for 24–48 hours. All tests were performed in duplicate, yielding a standard deviation (SD) of ± 0.7 mm [15; 16]. Ciprofloxacin 5 mcg, Vancomycin 10 mcg, Fluconazole 25 mcg (Himedia) were used as comparison drugs. The interpretation of susceptibility to comparators was carried out taking into account CLSI 2025 and EUCAST 2025.

Results and discussion. *Synthesis of title compounds*.

For the screening of antimicrobial activity, several functionally substituted anthraquinone derivatives were synthesized. Thus, 2-aminoanthracene-9,10-dione (**1**) was converted into the corresponding diazonium salt (**1.1**) according to previously reported procedures [17; 18]. Subsequently, as described in the Experimental section, the *in situ* generated diazonium salt was reacted with aminoacetonitrile, which resulted in the formation of a mixture of the corresponding compounds **2** and **4** (Scheme 1). The formation of these compounds

was confirmed by chromato-mass spectrometry. It was established that the yield of the target triazen compound **2** was 44% (m/z $[M+H]^+$ = 291.0), and that of the corresponding 2-anthracenedione-containing tetrazole was 28%. The isolated products were separated by thin-layer chromatography (TLC). The aromatic fragment of 2-(3-(9,10-dioxo-9,10-dihydroanthracen-2-yl) triaz-2-en-1-yl)acetonitrile **2** appears as multiplet at 7.70–8.20 ppm.

We also explored an alternative synthetic route to compound **4**, involving the cyclization of 2-(3-(9,10-dioxo-9,10-dihydroanthracen-2-yl)triaz-2-en-1-yl)acetonitrile (**2**) in an alcoholic medium (Scheme 2). The cyclization of the anthraquinone-based triazene proceeded smoothly under these conditions, affording the corresponding anthraquinone–triazole **4**. The structure of compound 4 was reliably established using a combination of IR, NMR, and chromatographic–mass spectrometric data. In the IR spectra, compound **4** shows characteristic features in the NH stretching region, which arise from prototropic NH ↔ N tautomerism within the 1,2,4-triazole ring rather than complete structural isomerization. Specifically, triazole 4 exhibits three NH absorption bands at 3410, 3320, and 3180–3240 cm^{-1}, reflecting the coexistence of different tautomeric forms. By comparison, the NH bands of its isomer are predicted to appear at 3360–3310, 3240–3180, and 3200–3100 cm^{-1}. Similar IR spectral patterns associated with tautomeric equilibria in anthraquinone-based azoles were observed in our previous studies [19; 20]. It should be noted that IR spectroscopy alone is insufficient for comprehensive structural elucidation; therefore, the assignment of compound **4** was based on consistent evidence obtained from complementary IR, NMR, and mass spectrometric analyses.

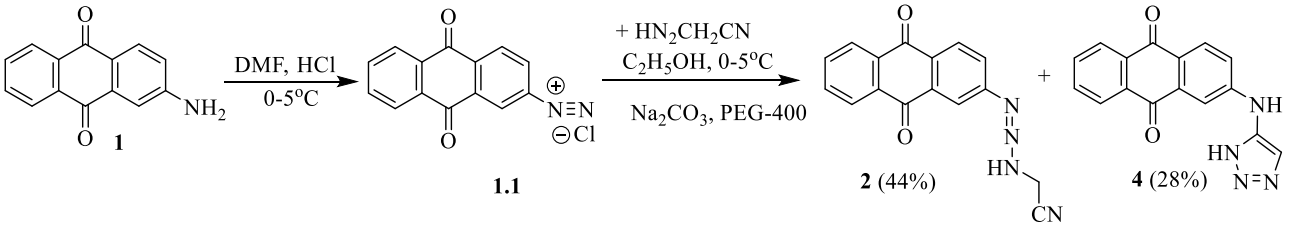
In addition, the IR spectra of the obtained triazoles show a medium-intensity band around 1645 cm^{-1}, presumably corresponding to C=C stretching vibrations in the triazole ring. Signals of the exocyclic NH proton in triazoles appeared as a broad singlet in a weak magnetic field at δ ~ 9.30–9.70 ppm, whereas the NH proton within the ring was observed further downfield in a weak magnetic field at δ ~ 14.50–14.80 ppm.

Continuing our studies, compound **5** was resynthesized according to our previous work [20] via a nucleophilic substitution reaction of bromaminic acid with butylamine as the nucleophilic agent (Scheme 3). The reaction was carried out in an aqueous medium using a bifunctional catalytic system composed of divalent iron and copper salts, which facilitates the substitution process and improves the overall yield of the target product.

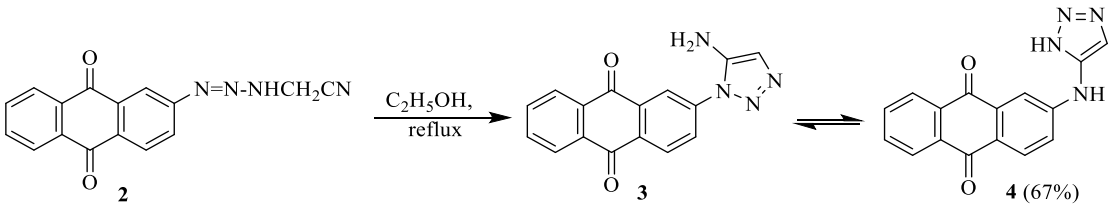
The antimicrobial activity of the synthesized compounds was evaluated (Table 1). Compound **5** demonstrated minor antimicrobial activity against biofilm-forming and non-biofilm-forming reference strains of Gram-positive microorganisms, specifically *Staphylococcus aureus subsp. aureus, reference biofilm-forming strain ATCC 25923* (195), and *Staphylococcus epidermidis*, reference non-biofilm-forming strain ATCC 12228 (193). This assessment is based on the observation of a partial growth inhibition zone (10 mm) in the agar diffusion assay, suggesting a slight bacteriostatic effect, and the high minimum inhibitory concentration (MIC > 1000 μg/mL), indicating low overall potency against these strains. No significant activity was observed against other tested Gram-positive or Gram-negative bacteria, confirming the limited spectrum of action of compound **5**.

Based on the results of the activity assessment of the hit compound **5** using the SwissADME database, it was established that the investigated compound exhibits favorable physicochemical parameters in all evaluated categories, including molecular weight, lipophilicity, solubility, and polarity [21]. The SwissADME bioavailability radar further confirmed its drug-likeness, with a bioavailability score of 0.55 units (Table 2).

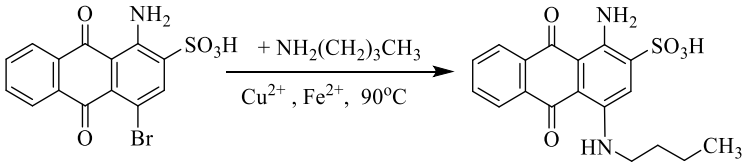
It should be noted that, based on the SwissADME analysis, compound **5** exhibits a low ability to cross the



Scheme 1



Scheme 2



5 (99%)

Scheme 3

Table 1
In vitro antimicrobial activity of synthesized compounds

	Zone of growth inhibition (mm ± SE)*													
	***Staphy-lococcus aureus* subsp. aureus ATCC 25923 biof-pos**	***Staphy-lococ-cus epidermidis* 12228 non-b**	***Strep-tococ-cus agalac-tiae* ATCC 13813**	***Entero-coccus* spp. (non-MDR) (2/4)**	***Staphy-lococcus aureus* B2**	***Pseudo-monas aerugi-nosa* ATCC 10145**	***Kleb-siella pneu-moniae***	***Klebsiel-la variicola***	***Klebsiel-la pneumo-niae***	***Raoul-tella ornithi-nolytica* DSM 7464 = ATCC 31898**	***Candi-da albi-cans***	***Candi-da albi-cans* 85**	***Aspergillus niger***	***Lactoba-cillus fermentum***
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	10± 0.2	10± 0.2	0	0	0	0	0	0	0	0	0	0	0	0
DMSO	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cip-rof-loxacin	10± 1.0	50± 1.2	50± 1.2	50± 1.2	0	20± 0.6	10± 0.2	0	15± 0.3	28± 0.4	–	–	-	50± 1.0
Vancomycin	10± 0.2	24± 0.6	25± 0.3	22± 0.3	0	–	–	–	–	–	–	–	-	-
Fluconazole	–	–	–	–	–	–	–	–	–	–	28± 0.6	15± 0.6	0	-

Table 2
Physicochemical properties, ADME parameters, pharmacokinetic characteristics, and drug-likeness descriptors of compound 5

Physicochemical properties	
Molecular weight	374.41
Number of heavy atoms	26
Number of aromatic heavy atoms	12
Number of rotatable bonds	5
Number of hydrogen bond donors	5
Number of hydrogen bond acceptors	3
Molar refractivity	97.74
TPSA Å²	134.94
Consensus log Po/w	2.21
Lipinski's rule of five	Yes
Pharmacokinetic parameters	
Gastrointestinal absorption	Low
Blood–brain barrier permeability (BBB)	No
P-gp substrate	No
Log Kp (SP) (cm/s) (skin permeability)	-6.26
Bioavailability score	0.55

blood-brain barrier. The assessment of the physicochemical properties of compound **5** also revealed certain unfavorable characteristics, particularly poor aqueous solubility.

Furthermore, the evaluation of medicinal chemistry parameters, namely PAINS, Brenk, and Lead-likeness structural alerts which identify toxic, chemically reactive, metabolically unstable fragments or those associated with unsatisfactory pharmacokinetic properties-indicated that compound **5** possesses some structural alerts due to the presence of anthraquinone, aniline, and sulfonic acid fragments in its structure.

On the other hand, these findings are not considered critical according to current criteria for drug development and can be optimized through rational structural modification.

Additional oral toxicity prediction using the ProTox III platform indicated that compound **5** belongs to toxicity class V (LD_{50} = 3350 mg/kg) (Table 3). However, the compound shows potential nephrotoxic, immunotoxic, and mutagenic warnings and therefore requires more thorough preliminary in vivo toxicity evaluation.

Experimental Part. Melting points were measured in open capillary tubes on an IA 9200 Electrothermal melting point apparatus (Bibby Scientific Limited, Stone, UK) and are uncorrected. The elemental analyses (C, H, N) were performed using the FlashSmart CHNS/O analyzer (Thermo Scientific, Waltham, MA, USA) and were within ±0.4% of the theoretical values. The ^{1}H and NMR spectra were recorded on Varian Gemini at 400 MHz) instrument in DMSO-d_6. Chemical shifts (δ) are quoted in ppm and coupling constants (J) are reported in Hz. LC-MS spectra were obtained on Ag-ilent 1260 Infinity II with single-quadrupole mass-selective detector Agilent 6125 (Agilent Technologies, Santa Clara, CA, USA). The reaction mixture was monitored by thin layer chromatography (TLC) using commercial glass-backed TLC plates (DC-Fertigfolien ALUGRAM Xtra SIL G/UV254, Germany) using eluents of different compositions. IR spectra were recorded on a spectrophotometer Specord M-80 (Carl Zeiss Industrielle Messtechnik GmbH, Jena, Germany) in KBr tablets. Solvents and reagents that are commercially available were used without further purification.

General procedure for the synthesis of a mixture of compounds 2 and 4.

Cyanomethylamine (0.015 mol) was dissolved in ethanol (20 ml), cooled to 0–5°C in an ice bath. Dioxoanthracenyldiazonium salt **1.1** (0.01 mol) was added with stirring, over 10–15 minutes. A 10% (w/v) aqueous solution of Na_2CO_3 was added dropwise under continuous pH monitoring to maintain the reaction medium at pH 7.5–8.0. Polyethylene glycol-400 was used as a reaction promoter at a molar ratio of cyanomethylamine to PEG-400 of 20:1. The temperature of the reaction mixture was raised to 60°C for 1 hour and filtered. The crude product was further purified by column chromatography on silica gel to afford individual compounds **2** and **4**, using o-xylene – acetone (4:6) as the eluent.

2-(3-(9,10-dioxo-9,10-dihydroanthracen-2-yl)triaz-2-en-1-yl)acetonitrile (2). Yield – 44%. M.p. 280°C. ^{1}H NMR (400 MHz, DMSO-d6): δ (ppm): 4.10 s (2H, CH_2), 7.70–8.20 m (6H, H), 8.80 s (1H, NH). ESI-MS m/z: 291 $[M + H]^+$.

*2-((1H-1,2,3-triazol-5-yl)amino)anthracene-9,10-dione (**4**).* Yield: 67%. Yellow crystals, m.p. > 300 °C. ^{1}H NMR (DMSO-d_6, δ ppm): 6.50 (s, 1H, CH), 7.30–8.20 (m, 7H, H), 9.30–9.70 (br s, 1H, NH), 14.50–14.80 (br s, 1H, NH). IR (KBr, cm^{-1}): 1630 (C=O), 1640 (C=N), 3150 (NH), 3550 (NH, triazole). ESI-MS m/z: 291 $[M + H]^+$.

*Alternative method of synthesis 2-((1H-1,2,3-triazol-5-yl)amino)anthracene-9,10-dione (**4**).* Cyanomethyltriazene 2 (0.005 mol) was refluxed in absolute ethanol (50–100 mL) for 1 hour. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting residue was purified and analyzed.

1-Amino-4-(butylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid (5) was resynthesized according to the procedure described in our previous work [15]. Its spectroscopic and physicochemical characteristics have been reported in detail in the same reference.

Conclusions. In this work, a series of functionally substituted anthracenedione derivatives, including triazene, triazole, and butylamino-substituted compounds, were synthesized and structurally characterized. The structures of the obtained compounds were confirmed by ^{1}H NMR spectroscopy, IR spectroscopy, and LC-MS analysis.

Screening of antimicrobial activity demonstrated that 1-amino-4-(butylamino)-9,10-dioxo-9,10-dihydroanthracene-2-sulfonic acid (compound 5) exhibited moderate activity against Gram-positive microorganisms Staphylococcus aureus and Staphylococcus epidermidis, including biofilm-forming strains, with an inhibition zone of approximately 10 mm. The observed activity was assessed relative to standard reference antimicrobial agents (ciprofloxacin, vancomycin, and fluconazole, Himedia). Under the same experimental conditions, the other tested compounds showed no detectable antimicrobial activity.

In silico analysis (SwissADME and ProTox III) indicated that compound **5** possesses acceptable physicochemical and pharmacokinetic properties, a reasonable bioavailability score (0.55), and belongs to toxicity

Table 3
Results of toxicity prediction for compound 5 using the ProTox III platform

Compound	LD_{50}	Toxicity Class	Type of toxicity					
			Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity
5	3350	5	Inactive	Inactive	Active	Inactive	Active	Active

class V (LD_{50} = 3350 mg/kg)). However, further optimization of its aqueous solubility and more detailed toxicological studies are required.

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Conflicts of interest: authors have no conflict of interest to declare.

АНТИМІКРОБНА ТА ПРОТИГРИБКОВА АКТИВНІСТЬ ДЕЯКИХ ПОХІДНИХ АНТРАЦЕНДІОНУ

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Мета – здійснити синтез ряду функціонально-заміщених похідних антрахінону, дослідити їх протимікробну активність, а також здійснити прогнозування лікоподібності одержаних сполук з використанням сучасних вебінструментів.
Матеріали і методи. У ході дослідження було використано стандартні методи органічного синтезу та проведено фізико-хімічний аналіз синтезованих сполук. Протимікробну активність досліджували з використанням методу дифузії в агар та методу серійних розведень відповідно до загальноприйнятих мікробіологічних протоколів. *In silico* скринінг лікоподібності синтезованих сполук здійснювали з використанням онлайн-сервісу SwissADME.
Результати й обговорення. У роботі синтезовано ряд нових функціонально-заміщених похідних антрахінону. За результатами скринінгу протимікробної активності було ідентифіковано сполуку-хіт 5, яка продемонструвала найвищий рівень активності серед досліджуваних сполук. Встановлено, що інші похідні антрацендіону не проявляють виражену антимікробну та фунгістатичну активність, що може бути пов'язано з особливостями їх хімічної будови. Отримані результати свідчать про перспективність подальших досліджень антрацендіонових похідних як потенційних антимікробних агентів.
Висновки. У роботі синтезовано та досліджено протимікробну активність чотирьох функціонально-заміщених похідних антрахінону. Встановлено, що сполука 5 проявляє протимікробну активність щодо Грам-позитивних мікроорганізмів, тоді як інші досліджувані сполуки за аналогічних умов активності не продемонстрували. *In silico* прогнозування лікоподібності та потенційної токсичності сполуки 5 з використанням сучасних вебінструментів показало прийнятні фармакокінетичні властивості та відсутність явних ознак токсичності. Отримані результати свідчать про перспективність подальших досліджень функціонально-заміщених похідних антрахінону як потенційних протимікробних агентів.
Ключові слова: заміщені антрахінони, синтез, протимікробна активність, SwissADME, ProTox III.
Конфлікт інтересів: відсутній.

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