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PRIMARY SCREENING OF THE BIOLOGICAL ACTIVITY OF HETEROCYCLIC AMINO- DERIVATIVES OF 2,3-DICHLORO-1,4-NAPHTOQUINONE

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Мета. Прояснити антимікробну та функціональну активності амінопіразольних похідних 2,3-дихлоро-1,4-нафтохінону та спрогнозувати їхню гостру токсичність. Матеріали та新陈代谢. Протимікробну активність гетероциклічних амінонохінних нафтохіну заздалегідь виявляли шляхом дифузії речовини в агар на твердому поживному середовищі та методом серійних розведення. Гостру токсичність для гризунів визначали методом моделювання QSAR, реалізованого в програмному забезпеченні GUSAR. Результати. У роботі досліджено антимікробну та функціональну активності нових гетероциклічних амінопіразольних нафтохіну, а також проведено визначення їх ін-сі відносна токсичності для шурів за чотирьох типах введення субстанції.

Висновки. Дослідження мікробіологічних похідних нафтохіну дозволило вивести сполуки, які проявляють високу антимікробну активність до зміночності Єшніна Candida temuis, а саме: 2-хлоро-3-((1-метил-1Н-піразол-4-ил)аміно)нафтален-1,4-діон 3а та 2-хлоро-3-((1-метил-1Н-піразол-3-ил)аміно)нафтален-1,4-діон 3В. Встановлено, що усі синтезовані сполуки проявляють відповідно бактеріостатичну активність. Визначено методом QSAR нетоксичну сполуку 3с при внутрішньочеревному шляху введення, а також нетоксичну сполуку 3д при підшкірному шляху введення. Ключові слова: амінопіразолохінні 2,3-дихлоро-1,4-нафтохінону, первинні біологічні скрипунці, програма GUSAR

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1 Introduction

Due to the increasing resistance of microorganisms to existing antimicrobial and fungicidal preparations, it is of great relevance to search for new biologically active compounds that could be used in the future for the production of low-toxic, microbial resistant drugs. That is why heterocyclic amino derivatives of naphthoquinone, which have a wide range of pharmacological activity, in particular, antibacterial [1, 2] antifungal [3], anticancer [4, 5], antiviral, anti-inflammatory and regenerating [6], occupy an important place among development of new drug substances.
The priority for today is the creation of new highly effective, low-toxic, antibacterial drugs as opposed to existing low-active ones. That is why research of new objects containing quinone and pyrazole fragments is an urgent task today.

Many sources of naphthoquinone derivatives that make up the class of natural compounds are listed in the literature: pigments, antibiotics, vitamins, co-enzymes [7–9]. Synthetic naphthoquinone compounds are the basis of antibacterial, antifungal, antitumor and antimalarial agents [1, 10, 11]. It has been reported that some heterocyclic amino derivatives of naphthoquinone have antifungal activity [3]. Synthetic thiol derivatives containing 1,4-naphthoquinone have been reported as potent antimicrobial and anticancer agents [2, 10]. However, the toxicity of naphthoquinone compared to antibacterial activity often prevents their use as drugs for the treatment of infectious diseases [12, 13].

It is also known that aminopyrazole derivatives are a component of effective drugs [14, 15]. Among them, a rare compound for the pyrazoles is the nucleoside antibiotic Pyrazofurin (1). Also noteworthy is the broad-spectrum lantibiotic Formicin (2) isolated from Bacillus paralicheniformis APC 1576. Effective non-steroidal anti-inflammatory drugs such as Celecoxib (3) and Butadione (Phenylbutazone) (4) also should be mentioned [16, 17, 20].

![Pyrazofurin](image1)

![Formicin](image2)

![Celecoxib](image3)

![Phenylbutazone](image4)

The introduction of an aminopyrazole fragments likely reduces toxicity and broadens the biological activity spectrum of the compounds.

The aim of our study is the primary screening of the biological activity of aminopyrazole naphthoquinone derivatives and in silico the determination of their acute toxicity in rats by four types of substance administration.

2. Planning (methodology) of research
The search for new antimicrobial and fungicidal agents is one of the important tasks of scientists of the present day, which are solved by the synthesis of new biologically active molecules [20].

To achieve this aim, the following tasks were set:
1) determine the biological activity of the first time synthesized compounds;
2) determine acute toxicity to rodents by the QSAR simulation method.

The following test strains were used for primary screening of biological activity carried out in accordance with WHO guidelines [18]: Escherichia coli, Staphylococcus aureus, Mycobacterium luteum and fungi: Candida tenuis, Aspergillus niger. The inoculum suspension was prepared using a Densi-La-Meter apparatus (manufactured by PLIVALachema, Czech Republic; wavelength 540 nm).

The suspension was prepared according to the device manual and information sheet No. 163-2006 "Standardization of preparation of microbial suspensions" (Kyiv) on innovations in health care system. The inoculum density was 109 cells (spores) / 1 ml compared to the McFarland Standard [19]. For antimicrobial evaluation we used Muller-Hinton agar. Antibacterial activity was assessed by measuring the zones of inhibition of the corresponding microorganism and compared with the zones of the reference preparations Nystatin (antimicrobial) and Vancomycin (fungicidal).

Acute rodent toxicity was determined by the QSAR simulation method using a free, accessible web service [http://www.pharmaexpert.com/GUSAR/AcuToxPredict/).

3. Materials and methods
Due to the special value of naphthoquinones and aminopyrazoles, the synthesis and research of new compounds containing both the pyrazole cycle and the quinoid bond system are of particular interest.

Antimicrobial and fungicidal activity studies were performed for newly synthesized naphthoquinone-containing nitrogen derivatives. The scheme and method of synthesis are shown in Fig. 1 [20].
The antimicrobial activity of the synthesized compounds 3a-d was studied by diffusion into agar on solid nutrient medium (beef agar extract for bacteria, wort agar for fungi). For all tested microorganisms, Petri dishes containing 20 ml of culture medium were used. The inoculum (microbial loading – 109 cells (spores) / 1 ml) was applied to the surface of solidified media and Whatman No. 1 filtered disks (6 mm diameter) impregnated with the test compounds (0.1 and 0.5 %) and placed on plates. The duration of bacterial incubation was 24 h at 35 °C and the incubation of fungi 48-72 h at 28–30 °C. The antimicrobial effect and the degree of activity of the tested compounds was evaluated by measuring the diameters of the zones of inhibition of growth of microorganisms (Table 1). Each experiment was repeated three times.

**Table 1**

Parameters of evaluation of results by the method of complex diffusion in agar

| No. | The diameter of the zone of inhibition of growth of microorganisms, mm | The degree of sensitivity of microorganisms |
|-----|---------------------------------------------------------------------|---------------------------------------------|
| 1.  | 11–15                                                               | low sensitivity                             |
| 2.  | 16–25                                                               | sensitive                                   |
| 3.  | >25                                                                 | highly sensitive                            |

**4. Results of the research**

The main results of the study of fungicidal activity of compounds 3a-d by the method of diffusion of the substance into agar (method A) are shown in Table 2.

**Table 2**

Fungibactericidal activity of test compounds (method A)

| Compound code | Concentration, % | The diameter of the zones of inhibition of growth of microorganisms, mm |
|---------------|------------------|-----------------------------------------------------------------------|
|               |                  | E.coli | S.aureus | M.luteum | C.tenuis | A.niger |
| 3a            | 0.5              | 0      | 15.4     | 13.0     | 24.0     | 20.0    |
|               | 0.1              | 0      | 7.4      | 0        | 20.0     | 17.0    |
| 3b            | 0.5              | 0      | 10.0     | 9.7      | 25.4     | 20.0    |
|               | 0.1              | 0      | 0        | 0        | 21.4     | 17.0    |
| 3c            | 0.5              | 0      | 0        | 10.0     | 0        | 0       |
|               | 0.1              | 0      | 0        | 7.0      | 0        | 0       |
| 3d            | 0.5              | 0      | 10.4     | 15.0     | 0        | 10.0    |
|               | 0.1              | 0      | 7.0      | 10.0     | 0        | 8.0     |
| C+            | 0.1              | 14.0   | 15.0     | 18.0     | 19.0     | 20.0    |

Note: C+: Vancomycin was used as a control in the antimicrobial activity tests of the synthesized compounds, and Nystatin was used in the antifungal activity tests.

Determination of the minimum bacteriostatic concentration (MBC) or minimum fungistatic concentration (MFC) was performed by serial dilution method (method B). The test substance was dissolved in DMSO to achieve the desired concentration. Next, a certain amount of the solution of the substance was introduced into the nutrient medium (meat-peptone broth for bacteria and unhilled beer must for fungi). The culture medium was inoculated with bacteria and fungi seed (microbial load of 106 cells (spores)/1 ml). Seed tubes were kept in a thermostat at the appropriate temperature (37 °C for bacteria; 30 °C for fungi) for 24–72 hours. The results were evaluated in the presence or absence of growth of microorganisms (according to the degree of microbial turbidity of the nutrient medium).
Bacterial test cultures were used to study the antimicrobial activity of the obtained compounds 3a-d: Escherichia coli, Staphylococcus aureus, Mycobacterium luteum and fungi: Candida tenuis, Aspergillus niger.

The gram-negative culture of *E. coli* bacteria was found to be resistant to the synthesized compounds 3a–3d at the tested concentration. The most active compounds against *C. tenuis* identified by the serial dilution method are compounds 3a (MIC=0.9 μg/ml, MFC=1.9 μg/ml) and 3b (MIC=7.8 μg/ml, MFC=15.6 μg/ml) (Table 4). The diameters of *C. tenuis* culture growth inhibition zones for these compounds at a concentration of 0.5 % were 24.0 mm and 25.0 mm, respectively, indicating the high sensitivity of this bacterial culture to the action of these compounds. This is higher than Nystatin. Compounds 3a, 3b, 3d showed moderate activity against the bacteria of the strain *A. niger* and *S. aureus*. Compared with Vancocycin, compound 3a at a concentration of 0.5 % showed the same activity against *S. aureus*. The other compounds 3b–d are less active.

It was also found that all of our tested compounds 3a–d showed moderate activity against bacteria of the *M. luteum* strain.

The results of the initial experimental microbiological studies indicate the selective bacterio- and fungistatic activity of the synthesized compounds (Tab. 3).

### Table 3

| No. | Compound code | *Escherichia coli* | Staphylococcus aureus | Mycobacterium luteum |
|-----|---------------|-------------------|----------------------|----------------------|
|     |               | MIC, μg/ml | MBC, μg/ml | MIC, μg/ml | MBC, μg/ml | MIC, μg/ml | MBC, μg/ml |
| 1.  | 3a            | +         | +        | 31.2      | 62.5        | 7.8        | 15.6        |
| 2.  | 3b            | +         | +        | 31.2      | 62.5        | 7.8        | 15.6        |
| 3.  | 3c            | +         | +        | +         | +          | 31.2      | 125.0       |
| 4.  | 3d            | +         | +        | 125.0     | 250.0       | 15.6      | 31.2        |

### Table 4

| No. | Compound code | *Candida tenuis* | Aspergillus niger |
|-----|---------------|-----------------|------------------|
|     |               | MIC, μg/ml | MFC, μg/ml | MIC, μg/ml | MFC, μg/ml |
| 1.  | 3a            | 0.9        | 1.9        | 0.9        | 15.6        |
| 2.  | 3b            | 7.8        | 15.6       | 7.8        | 31.2        |
| 3.  | 3e            | +          | +          | +          | +           |
| 4.  | 3d            | 250.0      | 500.0      | 62.5       | 250.0       |

*Note: «+» – no biocidal effect was observed in the tested concentrations (microbial growth was observed)*

The rodent acute toxicity assessment is an extremely important feature in the development of new drugs. However, given the relatively high cost of such experimental studies and ethical considerations, we used the prediction of acute toxicity of aminopyrazole naphthoquinonederivatives to rats using a free, accessible web service (http://www.pharmaexpert.ru/GUSAR/AcuToxPredict/) for various routes of administration of substances (intraperitoneal, intravenous, oral and subcutaneous). This is a method for modelling acute toxicity for QSAR rodents, implemented in GUSAR software [19]. Acute toxicity is an important adverse effect (or death) that occurs shortly after a single dose of the substance has started. The LD₅₀ value is one of the important characteristics of acute toxicity corresponding to a dose that causes 50 % mortality within 24 hours after administration of the substance. Acute toxicity, determined by external, oral or inhalation administration of the substance, is an important parameter for assessing overall toxicological risk, whereas acute toxicity for intra-intravenous and intravenous substance administration is an important parameter for drug development. There is a large amount of data in the literature and databases on the LD₅₀ of different compounds for rats, which enables the evaluation of LD₅₀ in silico using different QSAR methods [22]. The results of the studies are presented in Table 5. The results of the acute toxicity prediction show that the synthesized aminopyrazole derivatives of naphthoquinone can obviously be considered as low toxicity drugs (4, 5 class toxicity). In addition, the predicted data indicate that compound 3e is non-toxic in the intraperitoneal route of administration, and compound 3d is non-toxic in the subcutaneous route of administration.
1. phenyl-1H-pyrazole-3-carboxylate (3-chloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl)amino)naphthalene-1,4-dione compounds is 2-chloro-3-((1-methyl-1H-pyrazol-4-yl)amino)naphthalene-1,4-dione 3b, which exhibit a wide range of fungicidal activity and moderate bacterial culture activity of M. luteum strain. Ethyl-4-(((3-chloro-1,4-dioxo-1,4-dihydrophthal-2-yl)amino)-1-phenyl-1H-pyrazole-3-carboxylic acid 3d exhibits little fungicidal activity against test cultures, except E. coli, whose growth is not affected by any of our compounds. Moderate activity against bacteria of the M. luteum strain exhibits 2-chloro-3-((3-p-toly1)-1H-pyrazol-5-yl) amino)naphthalene-1,4-dione 3c.

When comparing the test compounds with the standards in the diameter of the zones of growth inhibition of microorganisms (Tab. 2) we found that compounds 3a and 3b have slightly higher fungicidal activity than Nystatin. The antifungal activity of compound 3a is similar to Vancomycin.

Conducted in silico toxicity spectrum studies of the compounds 3a – 3d under study indicate their predicted low toxicity. To confirm the predicted low toxicity of heterocyclic naphthoquinone derivatives, it is advisable to conduct further in vivo studies.

When comparing the fungicidal activity of the compounds studied by us with those of other naphthoquinone S-derivatives [2]: 2-chloro-3-[[3-(2-methylfuran-3-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino]naphthalene-1,4-dione, 2-[[4-aminosulfonyl-1,3-chloronaphthalene-1,4-dione and 2-chloro-3-[[3-(3-methylfuran-2-yl)-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl]amino]naphthalene-1 by 4-dione, it was found that S-substituted naphthoquinones exhibit high activity against S. aureus strain and low against C. tenuis and M. luteum strains. N-substituted naphthoquinones, on the contrary, are highly active against C. tenuis and M. luteum strains. This proves the relationship between the structure of the compounds and their activity.

\textbf{Study limitations.} When developing new drugs, it is important to assess their acute toxicity on rodents. However, such experimental studies are quite expensive, and they are constantly criticized for ethical reasons.

\textbf{Prospects for further research.} Therefore, the results of our studies indicate the need for further pharmacological screening of aminopyrazole derivatives of naphthoquinone in order to create new low-toxic antimicrobial and fungicidal agents based on them.

Given the informative nature of the screening results, it is possible to continue studying their activity against a larger sample of clinical strains of microorganisms. The properties of the basic structures thus identified need to be further optimized by the synthesis and investigation of a large number of their analogues.

\textbf{7. Conclusions}

The antimicrobial activity of aminopyrazole naphthoquinone derivatives was investigated and found that 2-chloro-3-((1-methyl-1H-pyrazol-4-yl)amino)naphthalene-1,4-dione (3a) and 2-chloro-3-((1-methyl-1H-pyrazol-3-yl)amino)naphthalene-1,4-dione (3b) exhibit high antimicrobial activity against Candida tenuis test culture. All the compounds tested do not affect the growth of bacteria of the genus Escherichia coli. The results of the initial experimental microbiological studies indicate the selective bacterio- and fungistatic activity of the nitrogen-containing heterocyclic naphthoquinone derivatives. The test compounds can be attributed to low-toxic drugs, and therefore it is advisable to conduct further experimental studies of these substances.

\textbf{Conflict of interests} Authors declare no conflict of interests

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