Synthesis, computational and antimicrobial studies of new 1,4-naphthoquinone aminothiazole derivatives

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The synthesis of new aminothiazole derivatives on the basis of substituted 1,4-naphthoquinones was carried out by the interaction of 2-R-3,6-dichloro-7-acylamino-1,4-naphthoquinones and potassium thiocyanate, 3,6-dichloro-2,7-diacylamino-1,4-naphthoquinone and diithiocyanate, of 2-R-3,6-dichloro-7-amino-1,4-naphthoquinones, 2-amino-7-nitro-3,6-dichloro-1,4-naphthoquinone and thiourea with the subsequent cyclization in aminothiazoles of 1,4-naphthoquinone. The physical and chemical properties of these compounds were determined, and the methods of their preparation are presented. The PASS computer program was used to predict the biological activity spectra of the new 1,4-naphthoquinone aminothiazole derivatives and to determine the most promising biological activities for experimental testing. Antibacterial and fungicidal activities were studied using the cultures of Staphylococcus aureus, Escherichia coli and Candida tenuis microorganisms. Some of the study compounds were found to have a moderate antibacterial and fungicidal activity, which in more than 90% of cases coincided with the computational predictions. The analysis of the structure–antimicrobial activity relationships provides recommendations for the design of the new derivatives. Some other biological activities have been predicted by PASS for these compounds, including antiviral, antineoplastic, immunomodulating, acute neurological disease treatment, antiparkinsonian, etc., which help to identify areas for the further research. Thus, the 1,4-naphthoquinone aminothiazole derivatives have been shown to be a promising class for the preparation of novel pharmacological agents with different applications.

Key words: naphthoquinone, thiocyanate, thiourea, thiazole, heterocyclization, biological activities, computational prediction, PASS computer program, antimicrobial action

Introduction

The thiazole ring system is a useful structural motif found in numerous biologically active molecules. This structure is utilized in developing drugs for the treatment of allergies [1], hypertension [2], inflammation [3], schizophrenia [4], bacterial [5] and HIV [6] infections. Aminothiazoles are known to be ligands of estrogen receptors [7] as well as a novel class of adenosine receptor antagonists [8], whereas other analogues are used as fungicides, inhibiting in vivo the growth of Xanthomonas and as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs [9].

Heterocyclic compounds based on of 1,4-naphthoquinone derivatives have many valuable properties and are used as antimicrobial, antitumor substances, dyes, catalysts, medications [10–12]. Therefore, taking into account their practical value, the synthesis of new S,N-containing heterocyclic compounds on the basis of 2,3,6,7-substituted 1,4-naphthoquinone, especially unknown in literature thiazole derivatives in positions 6 and 7, is a prospective task of the chemistry of biologically active compounds.

Materials and methods

The melting points were measured with a Nagem melting point apparatus and are uncorrected. 1H NMR spectra were recorded with a Varian VXR (300 MHz) spectrometer. The samples were prepared using DMSO-d6 as a solvent. The chemical shifts are expressed as δ, ppm relative to TMS. IR spectra were recorded with a Specord M80 using KBr tablets.

Materials. 2-R-3,6-dichloro-7-acylamino-1,4-naphthoquinone, 3,6-dichloro-2,7-diacylamino-1,4-naphthoquinone, 2-R-3,6-dichloro-7-amino-1,4-naphthoquinone, 2-amino-7-nitro-3,6-dichloro-1,4-naphthoquinone [13].
Methods for the synthesis of 2-amino-7-chloro-6-R-4-ynaphtho[2,3-d][1,3]thiazole-5,8-diones (3 a–e)

Method A. A mixture of 0.52 mmol of the corresponding 2-R-3,6-dichloro-7-acylamino-1,4-naphthoquinone 1 a–e and 0.05 g (0.52 mmol) of potassium thiocyanate in 30 ml of acetone was heated at constant stirring at 30–40 °C for 4 h. The reaction mixture was cooled to room temperature, and a 20 % NaOH solution was added. The reaction mixture was heated for 4 h and filtered after cooling (the filtrate containing sodium salt of 3 c or 3 e was acidified with 10 % HCl and filtered). The residue was recrystallized from acetonitrile.

Method B. A mixture of 1.5 mmol of the corresponding 2-N-R,3,6-dichloro-7-acylamino-1,4-naphthoquinone 6 a–e and 0.108 g (1.5 mmol) of thiourea in 30 ml of acetone was boiled at constant stirring for 4 h. The reaction mixture was cooled to room temperature, and a 20 % NaOH solution was added. The reaction mixture was heated for 4 h, then cooled and filtered (the filtrate containing sodium salt of 6 c or 6 e was acidified with 10 % HCl and filtered), and the residue was dried.

2-Amino-7-chloro-6-morpholin-4-ynaphtho[2,3-d][1,3]thiazole-5,8-dione (3a). Method B. Yield 85 %. Mₚ 173–175 °C.
IR v (cm⁻¹): 3530, 3460 (NH₂); 1680, 1640 (C=O).

¹H NMR (DMSO-d₆): δ: 3.00–3.18 (4H, m, CH₂); 3.62–3.70 (4H, m, CH₂); 7.35 (2H, broad s, NH₂); 8.50 (1H, s, CH₃ammon); 8.76 (1H, s, CH₃ammon).

Found, %: C 51.51; H 3.46; Cl 9.10; N 12.01; S 9.17. C₁₂H₂₃ClN₄O₄S₂.

2-Amino-7-chloro-6-piperidin-1-ynaphtho[2,3-d][1,3]thiazole-5,8-dione (3b). Method B. Yield 88 %. Mₚ 197–198 °C.

IR v (cm⁻¹): 3524, 3462 (NH₂); 1678, 1649 (C=O).

¹H NMR (DMSO-d₆): δ: 1.47–1.60 (4H, m, CH₂); 1.52–1.58 (2H, m, CH₂); 3.32–3.40 (4H, m, CH₂); 7.35 (2H, broad s, NH₂); 8.48 (1H, s, CH₃ammon); 8.76 (1H, s, CH₃ammon).

Found, %: C 55.25; H 4.08; Cl 10.19; N 12.08; S 9.22. C₁₂H₁₉ClN₄O₄S₂.

2-Amino-7-chloro-5,8-dioxo-5,8-dihydroxynaphto[2,3,d][1,3]thiazol-6-ylipiperidin-4-carboxylic acid (3c). Method B. Yield 86 %. Mₚ 207–208 °C.

IR v (cm⁻¹): 3534, 3431 (NH₂); 3000–2500 (COOH), 1760, 1678, 1660 (C=O).

¹H NMR (DMSO-d₆): δ: 1.73–1.92 (4H, m, CH₂); 2.49–2.57 (1H, m, CH); 4.24–4.32 (4H, m, CH₂); 8.29 (2H, s, NH₃); 8.48 (1H, s, CH₃ammon); 8.77 (1H, s, CH₃ammon); 12.36 (1H, broad, OH).

Found, %: C 52.11; H 5.10; Cl 3.60; N 10.72; S 8.18. C₁₂H₁₈ClN₄O₆S₂.

2-Amino-7-chloro-6-(dibutylamino)naphtho[2,3-d][1,3]thiazole-5,8-dione (3d). Method A. Yield 82 %. Mₚ 192–194 °C.

2-Amino-7-chloro-5,6-dioxo-5,6-dihydroxynaphtho[2,3,d][1,3]thiazol-5(4H)-one (8). Method A. Yield 35 %. Mₚ 152–153 °C.

IR v (cm⁻¹): 3467, 3441 (NH₂), 3367 (NH), 1690 (C=O). ¹H NMR (DMSO-d₆): δ: 3.37 (1H, s, SH); 7.43 (1H, s, CH₃ammon); 8.82 (1H, s, CH₃ammon); 9.30 (3H, s, NH₂, NH). 13C NMR (DMSO-d₆): δ: C 43.13; H 1.97; N 18.29; S 20.94. C₁₁H₁₂N₂O₄S₂.

Found, %: C 43.09; H 2.02; N 18.21; S 20.83.
2-Amino-7-mercapto-6-nitronaphtho[2,3-d][1,3]-thiazole-4,9-dione (9). Yield 12 %. M, 225–226 °C.
IR v (cm\(^{-1}\)): 3465, 3442 (NH\(_3\)), 1672, 1652 (C=O).
\(^1\)H NMR (DMSO-d\(_6\)) \&: 3.35 (1H, s, SH); 7.85 (2H, s, NH\(_2\)); 7.93 (1H, s, CH\(_{\text{ammon}}\)); 9.14 (1H, s, CH\(_{\text{ammon}}\)).
Calculated, %: C 42.99; H 1.64; N 13.67; S 20.87.
Found, %: C 43.03; H 1.61; N 13.63; S 20.83.

Results and discussion

Computer-aided prediction of biological activity spectra using PASS software

The prediction of the biological activity spectra of the synthesized compounds was performed employing the PASS computer program (Prediction of Activity Spectra for Substances) [14, 15]. The latest PASS version (2012 06 22) predicts 6400 kinds of biological activity based on the analysis of the training set including information about ~330000 drugs, drug-candidates, lead compounds, etc. The average prediction accuracy estimated in a leave-one-out cross-validation procedure for the whole training set is about 95 %. The PASS online version is freely available for scientific community on the website [16]. Based on PASS predictions, new pharmaceutical agents from diverse chemical classes with various kinds of biological activity have been discovered (for a review, see: [16, 17]).

PASS input information is presented by MOL or SD files with structural formulae of compounds under study; PASS output is presented by a list of probable activities with two estimated probabilities, Pa – the probability to be “active”; and Pi – the probability to be “inactive”.

The list of predicted activities for a certain chemical compound is called its biological activity spectrum. It includes the main and side pharmacological effects, (e. g., antihypertensive, hepatoprotective, sedative, etc.), the biochemical mechanisms of action, (\(\alpha\)-hydroxytryptamine agonist, acetylcholinesterase inhibitor, adenosine uptake inhibitor, etc.), specific toxicities (carcinogenic, hallucinogenic, hepatotoxic, etc.), antagonists (ATPase inhibitor, CYP3A4 inhibitor, HERG channel blocker, etc.), terms associated with drug metabolism (CYP1A substrate, CYP1A1 human substrate, CYP5A4 substrate, etc.), terms associated with the transport of drugs (P-glycoprotein substrate, P-glycoprotein inhibitor, P-glycoprotein inductor, etc.) and terms associated with gene expression (APOA1 expression enhancer, ErbB-2 expression inhibitor, etc.).

The higher the Pa value, the lower is the probability of obtaining false positives in biological testing. For example, if one selects for testing only compounds for which a particular activity is predicted with Pa > 0.9, the expected probability to find inactive compounds in the selected set is very low; however, about 90 % of active compounds are missed. If one lowers the Pa threshold to 0.8, the probability to find inactive compounds is still low, but (only) about 80 % of active compounds are missed, etc. PASS uses the criteria Pa = Pi as the default threshold, i. e. all compounds with Pa > Pi are declared as being active.

Another aspect of the predictions is the compounds’ novelty. If one limits oneself to high Pa values, one may find close analogues of known biologically active substances among the test compounds. For example, for Pa > 0.7, the chance to find the activity in experiment is high, but some of the activities may be a close analogue of the known pharmaceutical agents. If one chooses 0.5 < Pa < 0.7, the chance of obtaining activity in the experiment is lower, but the compounds may be less similar to the known pharmaceutical agents. For Pa < 0.5, the chance of obtaining activity in the experiment are even lower, but if the activity is found, the compound might happen to be a new chemical entity.

An example of the predicted pharmacological effects for compound 3e is given below (only data with Pa > 0.3 are shown):

<table>
<thead>
<tr>
<th>Pa</th>
<th>Pi</th>
<th>Pharmacological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.610</td>
<td>0.036</td>
<td>Acute neurologic disorders treatment</td>
</tr>
<tr>
<td>0.512</td>
<td>0.049</td>
<td>Urolithiasis treatment</td>
</tr>
<tr>
<td>0.429</td>
<td>0.037</td>
<td>Antineoplastic (astrocytoma)</td>
</tr>
<tr>
<td>0.414</td>
<td>0.027</td>
<td>Antibacterial</td>
</tr>
<tr>
<td>0.412</td>
<td>0.025</td>
<td>Immunomodulatory</td>
</tr>
<tr>
<td>0.396</td>
<td>0.171</td>
<td>Antiviral (Arbovirus)</td>
</tr>
<tr>
<td>0.307</td>
<td>0.083</td>
<td>Cell adhesion molecule inhibitor</td>
</tr>
<tr>
<td>0.301</td>
<td>0.080</td>
<td>Antifungal</td>
</tr>
<tr>
<td>0.409</td>
<td>0.197</td>
<td>Neuroprotector</td>
</tr>
<tr>
<td>0.356</td>
<td>0.150</td>
<td>Antiviral (Rhinovirus)</td>
</tr>
<tr>
<td>0.380</td>
<td>0.175</td>
<td>Potassium sparing diuretic</td>
</tr>
<tr>
<td>0.366</td>
<td>0.190</td>
<td>Antineoplastic (myeloid leukemia)</td>
</tr>
<tr>
<td>0.371</td>
<td>0.211</td>
<td>Antischemic, cerebral</td>
</tr>
<tr>
<td>0.342</td>
<td>0.192</td>
<td>Antinephrotic</td>
</tr>
<tr>
<td>0.354</td>
<td>0.237</td>
<td>Antineoplastic (genitourinary cancer)</td>
</tr>
<tr>
<td>0.340</td>
<td>0.262</td>
<td>Myasthenia Gravis treatment</td>
</tr>
<tr>
<td>0.327</td>
<td>0.280</td>
<td>Antineoplastic (oral cancer)</td>
</tr>
</tbody>
</table>

The most probable predicted activity for compound 3e is Acute neurologic disorders treatment (Pa = 0.610, Pi = 0.036), followed by Urolithiasis treatment (Pa = 0.512, Pi = 0.049), Antineoplastic (astrocytoma) (Pa = 0.429, Pi = 0.037), etc. In most cases, the Pa values are not close to the Pi values; therefore, only Pa values can be used to characterize the likelihood of activity.

If PASS predictions are analyzed for a set of compounds from a certain chemical series, the predicted activities can be defined as “typical”, i. e. are predicted for the majority of derivatives from this series, and “minor”, i. e. predicted only for some compounds [18].

Some predicted typical pharmacological effects for the seven compounds studied are shown in Table 1. These activities include antibacterial, antifungal, antiviral (arbovirus), antineoplastic, immunomodulatory, acute neurological disease treatment, and antiparkinsonian.

Two of the predicted activities (antibacterial and antifungal) were tested in biological experiments (see below).
Table 1. Typical activities predicted for new 1,4-naphthoquinone aminothiazole derivatives

<table>
<thead>
<tr>
<th>Compound ID</th>
<th>AB</th>
<th>AF</th>
<th>AV</th>
<th>AN</th>
<th>IM</th>
<th>ANDT</th>
<th>AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>0.33</td>
<td>–</td>
<td>–</td>
<td>0.53</td>
<td>0.50</td>
<td>–</td>
<td>0.40</td>
</tr>
<tr>
<td>3b</td>
<td>0.32</td>
<td>0.25</td>
<td>0.48</td>
<td>0.46</td>
<td>0.43</td>
<td>0.43</td>
<td>0.36</td>
</tr>
<tr>
<td>3c</td>
<td>0.41</td>
<td>0.30</td>
<td>0.40</td>
<td>0.43</td>
<td>0.41</td>
<td>0.61</td>
<td>0.24</td>
</tr>
<tr>
<td>3d</td>
<td>0.22</td>
<td>0.28</td>
<td>0.69</td>
<td>0.37</td>
<td>0.34</td>
<td>0.33</td>
<td>0.27</td>
</tr>
<tr>
<td>3e</td>
<td>0.32</td>
<td>0.26</td>
<td>0.69</td>
<td>0.51</td>
<td>0.37</td>
<td>0.38</td>
<td>0.21</td>
</tr>
<tr>
<td>5</td>
<td>0.32</td>
<td>0.20</td>
<td>0.65</td>
<td>0.76</td>
<td>0.36</td>
<td>0.36</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Note: AB = antibacterial; AF = antifungal; AV = antiviral (Arbovirus); AN = antineoplastic; IM = immunomodulator; ANDT = acute neurological disease treatment; AP = antiparkinsonian activity.

Interaction of 2-N-R,3,6-dichloro-7-acylamino-1,4-naphthoquinone with potassium thiocyanate and 3,6-dichloro-2,7-diacylamino-1,4-naphthoquinone with dithiocyanate

The synthesis of aminothiazoles 3 a–e was carried out similarly to the method described in literature [19, 20]. The corresponding thioyanate derivative 2 a–e appears in the interaction of potassium thiocyanate with 2-R,3,6-dichloro-7-acylamino-1,4-naphthoquinone 1 a–e in acetone for 30–40 °C (Method A). 2-Amino-7-chloro-6-R-4-yl-naphtho[2,3-d][1,3]-thiazole-5,8-diones 3 a–e were obtained at heating with a 20 % NaOH solution for 4 h (Scheme 1). To obtain 3 c, e, the filtrate containing sodium salt 3 c or 3 e was acidified with 10 % HCl and filtered.

![Scheme 1. Synthesis of 2-amino-7-chloro-6-R-4-yl-naphtho[2,3-d][1,3]-thiazole-5,8-diones 3 a–e](image)

An atom of carbon in position 6 of a molecule of 2-R,3,6-dichloro-7-acylamino-1,4-naphthoquinone 1 was activated by amino group acylation in position 7 [13]; this is why the nucleophilic anion of the thiocyanate group attacks this atom with the formation of 2, which converts into aminothiazole 3 in the presence of NaOH (Scheme 1). Compounds 3 a–e were obtained by Method A in 72–85 % yields.

The IR spectra of the obtained compounds 3 a–e have absorption bands in the interval 3431–3534 cm⁻¹, which are characteristic of the vibration of NH₂ groups. The 1680–1640 cm⁻¹ scope is characteristic of p-quinonic C=O groups. In the spectra of 6-thiocyanate-7-N-acylimonaphthoquinones 1 a–e [13], there are signals of NH group absorption in the area of 3310 cm⁻¹ and in the area of 2348 cm⁻¹ for the SCN group. Also, in the ¹H NMR of compounds 1 a–e [13], there are signals of acyl group protons in the area of 2.12–2.06 ppm, which are absent in the spectra of aminothiazole derivatives 3 a–e.

For the synthesis of diaminothiazole, we used dithiocyanate 5' obtained by the method described in [19]. In this case, the substitution of two chlorine atoms was realized; as a result, 2,7-diamino-1,8-dithio-3,6-diazocyclopentanaphthalene-4,10-dione (5) appeared in the presence of NaOH (Scheme 2).

![Scheme 2. Synthesis of 2,7-diamino-1,8-dithio-3,6-diazocyclopentanaphthalene-4,10-dione 5](image)
A comparison of $^1$H NMR spectra of compounds 3,6-dichloro-2,7-diacetyl-1,4-naphthoquinone 4 [13] and 5 shows the absence of signals of CH$_3$ group protons of the acyclic fragment in the area of 2.20–2.10 ppm; at the same time, signals of benzene cycle protons are almost identical (difference is 0.01 ppm) as compared with the spectrum of compound 4 where the signals of protons are present as two singlets at 8.76 and 8.31 ppm, respectively; this confirms formation of the aminothiazole cycle. In the IR spectrum of compounds 4 [13], a characteristic absorption band at 3200 cm$^{-1}$ of the amide group is present, and in the IR spectrum of compounds 5 absorption bands, which are characteristic of the vibration of the NH$_2$ group, were observed.

Interaction of 2-R-3,6-dichloro-7-amino-1,4-naphthoquinone and 2-amino-3,6-dichloro-7-nitro-1,4-naphthoquinone with thiourea

The interaction of 2-R-3,6-dichloro-7-amino-1,4-naphthoquinones 6 a–e with thiourea was carried out similarly to the method presented in [21]. We obtained aminothiazoles of 1,4-naphthoquinone 3 a–c (Method B), which did not require recrystallization (Scheme 3). To obtain 6 c, e, the filtrate containing a sodium salt of 6 c or 6 e was acidified with 10 % HCl and filtered.

![Scheme 3. Synthesis of 2-amino-7-chloro-6-R-4-yl-naphtho[2,3-d][1,3]-thiazole-5,8-diones 3 a–c](image)

In this case, cyclization takes place by the Hantzsch method [22]. In the process of the reaction, there is a nucleophilic attack by the sulphur atom on the halogen atom of carbon; as a result, we obtained isothioure intermediates, which in the presence of NaOH lead to the formation of aminothiazoles 3 a–c (Scheme 3).

Compounds 3 a–e were obtained by Method B with yields of 85–88 %. A comparison of methods for the synthesis of aminothiazoles 3 a–e has shown that Method A is suitable for the preparation of 3 d, e (82 %, 87 %, respectively), and Method B is convenient for obtaining 3 a–c (85–88 %).

The synthesis of aminothiazole derivatives of 2-amino-3,6-dichloro-7-nitro-1,4-naphthoquinone 7 [13] was carried out by the previously mentioned method. We obtained and identified the compounds as 2-amino-4-imino-8-mercaptop-7-nitroanphtho[1,2-d][1,3]thiazol-5(4H)-one 8 and 2-amino-7-mercaptop-6-nitroanphtho[2,3-d][1,3]-thiazole-4,9-dione 9 (Scheme 4) in low yields (35 % and 12 %, respectively) and a mixture of by-products which were difficult to divide and identify.

![Scheme 4. Interaction of 2-amino-3,6-dichloro-7-nitro-1,4-naphthoquinones with thiourea](image)

During the reaction, isothioure intermediates appear in positions 3 and 6 (Scheme 4). The mercaptonitroaminothiazole derivatives 2-amino-4-imino-8-mercaptop-7-nitroanphtho[1,2-d][1,3]thiazol-5(4H)-one (8) and 2-amino-7-mercaptop-6-nitroanphtho[2,3-d][1,3]-thiazole-4,9-dione (9) were obtained as a result of the action of KOH at heating. Depending on the isothioure group position 3 or 6, it can be hydrolysis to mercapto group (pos. 6) or cyclization to aminothiazole (pos. 3).

In the IR spectrum of compound 8, the absorption band attributed to the NH group was observed at 3367 cm$^{-1}$ and an intensive absorption band was identified in the area
of 1690 cm⁻¹, characteristic of the C=O group vibration. In the ¹H NMR spectra of 2-amino-4-imino-8-mercapto-7-nitronaphtho[1,2-d][1,3]thiazol-5(4H)-one 8 7.43–8.82 ppm regions, resonances of two benzene ring protons are present; furthermore, spectral lines characteristic of NH₂, NH and SH groups are also present. In the IR spectrum of 2-amino-7-mercapto-6-nitronaphtho[2,3-d][1,3]-thiazole-4,9-dione 9, two absorption bands characteristic of p-quinonic C=O groups were observed at 1652, 1672 cm⁻¹, and an absorption band of the NH₂ group was present in the region of 3442, 3465 cm⁻¹. In ¹H NMR spectrum of compound 9, a signal of the SH group proton at 3.35 ppm was noted.

The structure of the newly obtained mercaptoaminothiazoles 8 and 9 of naphthoquinone was also confirmed by qualitative reactions of the free SH group.

The reaction mixture of 8, 9 after evaporation of the solvent in vacuum was divided on a chromatographic column (eluent – benzene : chloroform, 2 : 1). Compounds 8 and 9 were selected in a 3 : 1 correlation.

Thus, new aminothiazole derivatives not described in the literature were synthesized by the reaction of 2,3,6,7-substituted 1,4-naphthoquinones with thiocyanate and thiourea. The obtained compounds open possibilities for obtaining of new derivatives with a wide spectrum of biological activity.

Table 2. Antibacterial and antifungal activity of the synthesized compounds

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Compound</th>
<th>Diameter of inhibition zone, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3a</td>
<td>3b</td>
</tr>
<tr>
<td>E. coli</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S. aureus</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>C. tenuis</td>
<td>16</td>
<td>17</td>
</tr>
</tbody>
</table>

Data presented in Table 2 show that S. aureus has a high sensitivity to compounds 5 and 9 in comparison with oxacillin and DCNQ, which exert a selective action on gram-positive bacteria. The majority of the compounds showed a higher antimicrobial action on gram-positive bacteria than did DCNQ and oxacillin. The absence of inhibition zones of E. coli bacteria has shown that the study compounds at these concentrations have no antibacterial action. E. coli appeared to be sensible to compounds 5 and 9, at the same time oxacillin had not antimicrobial activity as regards this culture. Compound 9 had a higher inhibition zone than DCNQ for the action on gram-negative bacteria (Fig.1).

The structure of all obtained aminothiazole naphthoquinone derivatives was confirmed by element analysis, ¹H NMR and IR spectral data.

Antibacterial and antifungal activity of the synthesized compounds

The antimicrobial activity was studied by the disk method, using the following cultures of microorganisms: Staphylococcus aureus, Escherichia coli, and Candida tenuis.

All cultures were grown at 37 °C in the medium with peptone, yeast extract. Disks (5 mm in diameter) were soaked in 0.02 mg ml⁻¹ of thiols as solutions in DMF. A disk was put on an exponentially growing plated culture with the appropriate dilution to 10⁶ cells per ml. The plates were then incubated for 24 h at 37 °C. The results were recorded by measuring the zones surrounding the disk. Control disks contained DCNQ (2,3-dichloro-1,4-naphthoquinone) and oxacillin [23–26].

The antibacterial and antifungal activities were estimated by the size of the diameter of inhibition zones of microorganisms’ growth.

Most of the compounds were found to show a moderate antibacterial and antifungal activity (Table 2), and some substances superseded the reference drugs (oxacillin and DCNQ).

![Fig. 1. Antimicrobial action of the synthesized compounds](image-url)
It was established that the synthesized compounds 3e and 9 showed an antifungal activity higher than that of DCNQ.

On the basis of data presented in Table 2, the following conclusions as to the structure – antimicrobial activity relationships can be done:

for bacteria: $9 > 5 > 3d > 3e > 3c > 3a > 3b$;

for fungi: $9 > 3e > 3c > 3d > 3a > 3b > 5$.

Therefore, as a result of our experimental studies, we have confirmed the computational prediction of antibacterial and antifungal activities for the study compounds on S. aureus, E. coli and C. tenuis cultures. Since the $Pa$ values estimate the probability of belonging to the class of “actives”, there is no correlation between the $Pa$ values and the diameters of the inhibition zone, which characterize the potency of the compounds.

Conclusions

For the first time, new aminothiazole derivatives of 2,3,6,7-substituted 1,4-naphthoquinones have been synthesized. The physical and chemical properties of these compounds have been determined, and the methods of their preparation are presented.

Using the PASS computer program the biological activity spectra of the synthesized compounds have been estimated. Among the effects that were predicted as typical of this chemical series there are antibacterial, antifungal, antiviral (arbovirus), antineoplastic, immunomodulator, acute neurological disease treatment, and antiparkinsonian activities.

The experimental testing of the antimicrobial action of the study compounds on the S. aureus, E. coli and C. tenuis cultures have confirmed these two activities to be typical of this chemical series. The activity of some 1,4-naphthoquinone aminothiazole derivatives supersedes that of the reference drugs oxacillin and DCNQ.

Since the results of computational predictions regarding antibacterial and antifungal activities were confirmed in more than 90% of cases, the other biological activities predicted for 1,4-naphthoquinone aminothiazole derivatives deserve further studies.

References


NAUJŲ 1,4-NAFTOCHINONO AMINOTIAZOLO DARINIŲ SINTEZĖ, BIOLOGINIO AKTYVUMO PROGNOZAVIMAS IR ANTIMIKROBINIŲ SAVYBIŲ TYRIMAS

Santrauka

2-R-3,6-Dichlor-7-acilamino-1,4-naftochinonų ir kalio tiocianato, 3,6-dichlor-2,7-diacilamino-1,4-naftochinono ir ditiocianato, 2-R-3,6-dichlor-7-amino-1,4-naftochinonų, 2-amino-7-nitro-3,6-dichlor-1,4-naftochinono ir tiokarbamido tarpusavio reakcijų metu gauti nauji 1,4-naftochinono aminotiazolo dariniai, nustatytos jų fizikinės ir cheminės savybės. Naudojant kompiuterinę programą PASS įvertintas prognozuojamas susintetintų junginių biologinis aktyvumas, atlikti jų biologiniai tyrimai. Įtirtas antibakterinis ir priežiūrinis poveikis Staphylococcus aureus, Escherichia coli ir Candida tenuis mikroorganizmams ir nustatyta, kad dalis tiriamųjų junginių pasižymi vidutiniu aktyvumu, daugiau nei 90 proc. sutampančiu su kompiuteriniais duomenimis. Junginio struktūros ir antimikrobinio aktyvumo ryšio analizė suteikia galimybę sintetinti naujas darinius. Taikant PASS metodą, taip pat įvertintos galimos susintetintų junginių antivirusinės, antineoplastinės, imunomodulatorių savybės, jų tinkamumas neurologinėms, Parkinsono ligoms gydymui. Gauti duomenys leidžia daryti prielaidą, kad 1,4-naftochinono aminotiazolų dariniai yra perspektyvūs vaistiniai preparatai.