Synthesis of New 6,7(N,O)-Heterocyclic 1,4-Naphthoquinones

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1. Introduction

The amino acid derivatives of 1,4-naphthoquinone have a high bacteriostatic, bactericidal [1-6], antiviral, antiphthisic, antibiotic [7-12], antimalarial activity [13,14], antihypoxic, antiplatelet [15,16], antiplasmodial [17], antianginal antiischemic [18,19] and antitumor activity [20-25] and can be used as pharmacological drugs in medicine and also as fungicides and insecticides [26-29].

Compounds of this order are used as physiologically active substances. Besides, they can be used as subsequent transformations, including synthesis of heterocyclic derivatives on their basis.

2. Materials and Methods


Melting points were measured on a Nagema melting point apparatus and are uncorrected. 1H NMR spectra were recorded on Varian VXR (400 MHz) spectrometer as a solution in DMSO-d6 with TMS as an internal standard. 13C NMR spectra were recorded on Bruker WP-200 (50.327 MHz) spectrometer as a solution in DMSO-d6. IR spectra were recorded on Specord M80 in tablets KBr.

General procedure of synthesis (2 a-i): 10 mmole of amino-1,4-naphthoquinone (1 a-i) suspended with 5-7 ml of acetic anhydride and 2-3 drops of H2SO4. The reaction mixture was stirred for 3 h., and the solvent was evaporated by vacuum. The residue was diluted by water, filtered, dried, and recrystallized from toluene, yield 72-79%. All other compounds of this series were synthesized by following the above procedure.
N-[3-(acetylamino)-7-chloro-6-morpholin-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-glycine (2a C₁₈H₁₈ClN₃O₆) 1H NMR (400 MHz, DMSO-d₆) 9.73 (1H, s, NH); 8.53 (1H, s, CH₂); 7.85 (1H, s, CH₃); 4.12 (2H, s, CH₂); 3.70-3.62 (8H, m, CH₂); 2.47 (3H, s, CH₃); IR 3200 (NH); 1688,1648 (C=O); 13C NMR (100 MHz, DMSO-d₆) δ = 179.21, 178.24, 171.32, 170.53, 153.65, 147.49, 132.18, 129.29, 127.76, 122.34, 114.45, 110.56, 67.23, 49.82, 45.33, 25.63 ppm.

N-[3-(acetylamino)-7-chloro-6-piperidin-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-glycine (2b C₂₁H₂₁ClN₃O₅S) 1H NMR (400 MHz, DMSO-d₆) 9.71 (1H, s, NH); 8.52 (1H, s, CH₃); 7.84 (1H, s, CH₃); 4.14 (2H, s, CH₂); 3.42-3.33 (4H, m, CH₂); 2.45 (3H, s, CH₃); 1.60-1.53 (6H, m, CH₂); IR (KBr, v_max/sm⁻¹) 3205 (NH); 1693,1650 (C=O);

N-[3-(acetylamino)-7-chloro-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-glycine (2c C₂₅H₂₄ClN₃O₅) 1H NMR (400 MHz, DMSO-d₆) 9.68 (1H, s, NH); 8.57 (1H, s, CH₃); 7.84 (1H, s, CH₃); 4.11 (2H, s, CH₂); 3.61 (4H, t, CH₂); 2.48 (3H, s, CH₃); 1.91-1.87 (4H, m, CH₂); 1.42-1.34 (4H, m, CH₂); 0.92 (6H, t, CH₃); IR (KBr, v_max/sm⁻¹) 3215 (NH); 1685,1645 (C=O);

N-[3-(acetylamino)-7-chloro-6-methionine-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-methionine (2d C₁₉H₂₀ClN₃O₅S) 1H NMR (400 MHz, DMSO-d₆) 9.58 (1H, s, NH); 8.46 (1H, s, CH₃); 8.02 (1H, d, CH₃); 4.60-4.57 (H, m, CH); 3.73-3.60 (8H, m, CH₂); 2.60-2.58 (2H, m, CH₂); 2.46 (3H, s, CH₃); 2.42-2.17 (2H, m, CH₂); 2.08 (3H, s, CH₃); IR (KBr, v_max/sm⁻¹) 3180 (NH); 1675, 1660 (C=O); 13C NMR (100 MHz, DMSO-d₆) δ = 180.65, 179.21, 178.24, 171.32, 154.72, 147.49, 132.18, 129.48, 127.95, 122.88, 114.45, 111.10, 67.23, 52.59, 49.82, 32.41, 30.43, 25.63, 15.17 ppm.

N-[3-(acetylamino)-7-chloro-6-piperidin-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-methionine (2e C₂₂H₂₆ClN₄O₅S) 1H NMR (400 MHz, DMSO-d₆) 9.67(1H, s, NH); 8.44 (1H, s, CH₃); 8.01 (1H, d, CH₃); 4.61 (H, m, CH); 3.40-3.32 (8H, m, CH₂); 2.61-2.57 (2H, m, CH₂); 2.47 (3H, s, CH₃); 2.44-2.15 (2H, m, CH₂); 2.07 (3H, s, CH₃); 1.63-1.51 (6H, m, CH₂); IR (KBr, v_max/sm⁻¹) 3180 (NH); 1675, 1660 (C=O);

N-[3-(acetylamino)-7-chloro-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-methionine (2f C₂₆H₃₂ClN₄O₅S) 1H NMR (400 MHz, DMSO-d₆) 9.78 (1H, s, NH); 8.49 (1H, s, CH₃); 8.00 (1H, d, CH₃); 4.57 (1H, m, CH); 3.65-3.60 (4H, m, CH₂); 2.61-2.57 (2H, m, CH₂); 2.07 (3H, s, CH₃); 1.93-1.86 (4H, m, CH₂); 1.44-1.36 (4H, m, CH₂); 0.94(6H, t, CH₃); IR (KBr, v_max/sm⁻¹) 3222 (NH); 1670, 1655 (C=O);

N-[3-(acetylamino)-7-chloro-6-methionine-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-phenylalanine (2g C₂₈H₃₀ClN₄O₆S) 1H NMR (400 MHz, DMSO-d₆) 9.86 (3H, s, NH, OH); 8.52 (1H, s, CH₃); 7.85 (1H, d, CH₃); 7.53-7.46 (4H, m, CH₂); 7.42-7.38 (2H, m, CH₂); 7.13-7.05 (4H, m, CH₂); 4.74-4.70 (H, m, CH); 3.72-3.60 (8H, m, CH₂); 3.30-3.20 (2H, m, CH₂); 2.45 (3H, s, CH₃); IR (KBr, v_max/sm⁻¹) 3232 (NH); 1695,1645 (C=O); 13C NMR (100 MHz, DMSO-d₆) δ = 179.21, 179.02, 178.24, 171.32, 154.10, 147.49, 132.18, 129.16, 129.05, 127.90, 127.18, 122.51, 114.45, 110.73, 67.23, 53.75, 49.82, 39.60, 25.63 ppm.

N-[3-(acetylamino)-7-chloro-6-piperidin-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-phenylalanine (2h C₂₉H₃₂ClN₅O₇S) 1H NMR (400 MHz, DMSO-d₆) 9.85 (3H, s, NH, OH); 8.50 (1H, s, CH₃); 7.86 (1H, d, CH₃); 7.51-7.48 (4H, m, CH₂); 7.41-7.37 (2H, m, CH₂); 7.12-7.09 (4H, m, CH₂); 4.72-4.70 (H, m, CH); 3.39-3.32 (4H, m, CH₂); 3.29-3.21 (2H, m, CH₂); 2.48 (3H, s, CH₃); 1.57-1.48 (6H, m, CH₂); IR (KBr, v_max/sm⁻¹) 3232 (NH); 1695,1645 (C=O);

N-[3-(acetylamino)-7-chloro-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydronaphtalen-2-yl]-phenylalanine (2i C₂₀H₂₈ClN₃O₅S) 1H NMR (400 MHz, DMSO-d₆) 9.78 (3H, s, NH, OH);
8.55 (1H, s, CH₆); 7.83 (1H, d, CH₆); 7.52-7.47 (4H, m, CH₂); 7.40-7.35 (2H, m, CH₂); 7.10-7.07 (4H, m, CH₂); 4.72-4.68 (H, m, CH); 3.64-3.61 (4H, m, CH₂); 3.32-3.25 (2H, m, CH₂); 2.45 (3H, s, CH₃); 1.95-1.87 (4H, m, CH₂); 1.45-1.31 (4H, m, CH₂); 0.92(6H, t, CH₃); IR (KBr, νmax/sm⁻¹) 3240 (νH); 1680,1655 (C=O);

General procedure of synthesis (3 a-i): To the suspension (30 mmole) of acylaminoo-1,4-naphthoquinone (2 a-i) in 30ml of ethanol it was added 1.2 g of NaOH (30 mmole) in 7 ml of water, left at boiling during 2-3 h., reactionary mixture was chilled to the room temperature, filtered, the residue was crystallized from acetoneitrile, yield 62-75%. All other compounds of this series were synthesized by following the above procedure.

[(7-chloro-2-methyl-6-morpholin-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl)-acetic acid] (3a C₁₈H₁₆ClN₄O₅) ¹H NMR (400 MHz, DMSO-d₆) δ 9.22 (1H, s, CH₆); 9.11 (1H, s, CH₆); 8.50 (1H, s, OH); 4.89 (2H, s, CH₂); 3.70-3.62 (8H, m, CH₂); 2.63 (3H, s, CH₃); IR (KBr, νmax/sm⁻¹) 3000-2500 (COOH) 1684, 1660 (C=O); ¹³C NMR (100 MHz,DMSO-d₆) δ = 179.21, 178.24, 168.26, 157.25, 147.49, 145.97, 143.60, 129.98, 129.31, 127.34, 114.45, 95.55, 67.23, 49.82, 46.96, 12.44 ppm.

[(7-chloro-2-methyl-6-piperidin-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl)-acetic acid] (3b C₁₇H₁₄ClN₅O₅S) ¹H NMR (400 MHz, DMSO-d₆) δ 9.23 (1H, s, CH₆); 9.10 (1H, s, CH₆); 8.50 (1H, s, OH); 4.89 (2H, s, CH₂); 3.40-3.32 (4H, m, CH₂); 2.63(3H, s, CH₃); 1.59-1.51 (6H, m, CH₂) IR (KBr, νmax/sm⁻¹) 3000-2500 (COOH), 1687, 1665(C=O); ¹³C NMR (100 MHz,DMSO-d₆) δ = 179.21, 178.24, 168.26, 157.25, 147.49, 145.97, 143.60, 129.98, 129.31, 127.34, 114.45, 95.55, 67.23, 49.82, 46.96, 12.44 ppm.

[(7-chloro-2-methyl-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl)-acetic acid] (3c C₂₅H₂₄ClN₅O₅S) ¹H NMR (400 MHz, DMSO-d₆) δ 9.21 (1H, s, CH₆); 9.15 (1H, s, CH₆); 8.50 (1H, s, OH); 4.89(2H, s, CH₂); 3.63 (4H, t, CH₂); 2.63(3H, s, CH₃); 1.93-1.86 (4H, m, CH₂); 1.44-1.35 (4H, m, CH₂); 0.94 (6H, t, CH₃); IR (KBr, νmax/sm⁻¹) 3000-2500 (COOH), 1674, 1658(C=O); ¹³C NMR (100 MHz,DMSO-d₆) δ = 179.21, 178.24, 167.84, 165.39, 147.49, 145.04, 144.14, 130.17, 129.31, 127.54, 114.45, 96.09, 67.23, 53.65, 49.82, 32.17, 29.37, 15.07, 12.86 ppm.

[(2-[7-chloro-2-methyl-6-morpholin-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl]-4-(methylthio)butanoic acid] (3d C₁₉H₁₉ClN₅O₄) ¹H NMR (400 MHz, DMSO-d₆) δ 9.46 (1H, s, OH); 9.38 (1H, s, CH₆); 9.04 (1H, s, CH₆); 5.33 (1H, t, CH); 3.70-3.62 (8H, m, CH₂); 2.67 (3H, s, CH₃); 2.65-2.64 (4H, m, CH₂); 2.46-2.40 (4H, m, CH₂); 2.02 (6H, s, CH₃); IR (KBr, νmax/sm⁻¹) 3000, 2500 (COOH) 1678, 1661 (C=O); ¹³C NMR (100 MHz,DMSO-d₆) δ = 179.21, 178.24, 167.84, 165.39, 147.49, 145.04, 144.14, 130.17, 129.31, 127.54, 114.45, 96.09, 67.23, 53.65, 49.82, 32.17, 29.37, 15.07, 12.86 ppm.

[(2-[7-chloro-2-methyl-6-piperidin-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl]-4-(methylthio)butanoic acid] (3e C₂₁H₂₃ClN₅O₄S) ¹H NMR (400 MHz, DMSO-d₆) δ 9.46 (1H, s, OH); 9.38 (1H, s, CH₆); 9.02 (1H, s, CH₆); 5.33 (1H, t, CH); 3.40-3.32 (4H, m, CH₂); 2.67(3H, m, CH₃); 2.65-2.64 (2H, m, CH₂); 2.46-2.40 (2H, m, CH₂); 2.02 (3H, s, CH₃); 1.59-1.51 (6H, m, CH₂) IR (KBr, νmax/sm⁻¹) 3000-2500 (COOH) 1675, 1654 (C=O); ¹³C NMR (100 MHz,DMSO-d₆) δ = 179.21, 178.24, 167.84, 165.39, 147.49, 145.04, 144.14, 130.17, 129.31, 127.54, 114.45, 96.09, 67.23, 53.65, 49.82, 32.17, 29.37, 15.07, 12.86 ppm.

[(2-[7-chloro-2-methyl-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl]-4-(methylthio)butanoic acid] (3f C₂₅H₃₀ClN₅O₄S) ¹H NMR (400 MHz, DMSO-d₆) δ 9.46 (1H, s, OH); 9.38 (1H, s, CH₆); 9.07 (1H, s, CH₆); 5.35 (1H, t, CH); 3.63 (4H, t, CH₂); 2.67(3H, s, CH₃); 2.65-2.64 (2H, m, CH₂); 2.46-2.42 (2H, m, CH₂); 2.02 (3H, s, CH₃); 1.93-1.86 (4H, m, CH₂); 1.44-1.36 (4H, m, CH₂); 0.94 (6H, t, CH₃); IR (KBr, νmax/sm⁻¹) 3000-2500 (COOH) 1672, 1663 (C=O);
(2-[7-chloro-2-methyl-6-morpholine-4-yl-5,8-dioxo-5,8-dihydro-1N-naphtho[2,3-d]imidazol-1-yl]-3-phenylproanoic acid) (3g C₂₂H₂₅ClN₃O₄) ¹H NMR (400 MHz, DMSO-d₆) δ = 179.21, 178.24, 158.88, 148.99, 147.49, 144.33, 136.75, 128.99, 128.97, 128.91, 126.35, 114.45, 96.28, 67.23, 49.82, 43.99, 33.17, 13.25 ppm. ¹³C NMR (100 MHz, DMSO-d₆) δ = 1690, 1685 (C=O). Tested microorganisms included the following bacteria: Staphylococcus aureus, Escherichia coli, and Bacillus subtilis. All bacteria grew at 37°C in a medium with peptone, yeast extract. Disks (5 mm diameter) were soak soaked in 0.02 mg mL⁻¹ of compounds as solutions in DMF. The disk was put on an exponentially growing plated culture with appropriate dilution to 1.0×10⁶ colony-forming units. The plates were then incubated for 24 h at 37°C. The results

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were recorded by measuring the zones surrounding the disk. Control disks containing DCNQ and oxacillin.

3. Results and Discussion

With the purpose of the creation of new imidazole systems of 1,4-naphthoquinone, we used previously synthesized 2-R-3-chloro-7-acylamino-1,4-naphthoquinone (2 a-i) which were obtained by acylation of 2-R-3-chloro-7-amino-1,4-naphthoquinones (1 a-i) by acetic anhydride in the presence of the catalytic amount of H2SO4, which there is as acylation agent and as a solvent. Heating of substances (2 a-i) in ethanol in the presence of an equivalent amount of NaOH in the mild conditions there is lead to cyclization in imidazole derivatives (3 a-i) (Scheme 1).

Oxazoles of type (4 a-c), were obtained by the interaction of 2,6-R-3-chloro-7-amino-1,4-naphthoquinone (1 a-i) in the medium of acetic anhydride with the catalytic amount of concentrated H2SO4 and heating at 50-60°C during 5-7 h. [30, 31].

In 1H NMR spectrums of compounds (4 a-c) there are present signals: 8,91 (1H, s, CH₉); 8,73 (1H, s, CH₉); 2,61 (3H, s, CH₃). In the IR spectrum of these compounds, the intensive absorption bands at 1680, 1660 cm⁻¹ are typical for p-quinonic C=O groups.

The results of element analysis, TLC, 1H NMR - and IR -spectroscopy confirmed the synthesized compounds' structure.

So, we investigated that the amino derivatives of 1,4-naphthoquinone in an alkaline medium environment under mild conditions form imidazole derivatives. Elimination of amino substitutes in the 6 position with the oxazole cycle formation in the acidic medium at heating is observed.

Antibacterial and fungicide activity was studied using the disk method [32-37], using the following cultures of microorganisms: Staphylococcus aureus, Escherichia coli, and Candida tenuis. As controls, there were used DCNQ (2,3-dichloro-1,4-naphthoquinone) and oxacillin. Antibacterial and fungicide activity was estimated by diameter of inhibition zones of growth of microorganisms.
As a result of the carried out screening, it was established that part of the compounds has moderate antibacterial and fungicide activity, but there are some substances with high activity (Table 1).

Table 1. Data of antibacterial and fungicide activity of the synthesized compounds

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<th>3b</th>
<th>3c</th>
<th>3d</th>
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<th>3g</th>
<th>3h</th>
<th>3i</th>
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<th>4b</th>
<th>4c</th>
<th>DCNQ</th>
<th>Oxacillin</th>
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S. aureus and C. tenuis are susceptible to compounds (4 a-c), and they have moderate sensitivity to compounds (3 a-i) in comparison to oxacillin and DCNQ, which have a selective action on gram-positive bacteria. The absence of inhibition zones of E.coli showed that the investigated compounds in these concentrations don’t have an antibacterial action in relation to gram-negative bacteria. E.coli appeared sensitive to compounds (4 a-c), while oxacillin doesn’t have antimicrobial activity in relation to this culture.

Therefore, the carried-out investigations allowed us to find the compounds among investigated heterocyclic derivatives of 1,4-naphthoquinone (4 a-c) with high activity in relation to the cultures of S. aureus, E. coli, and C. tenuis, which have higher antimicrobial activity in comparison with the standards. The results of the research allow continuing the search of preparations in this order of compounds.

4. Conclusions

Thus, we investigated that in heterocyclization reactions of amino derivatives of 1,4-naphthoquinone in an alkaline medium, imidazole derivatives are formed under mild conditions. In an acidic environment, an amine substituent is cleaved at the 6th position to form an oxazole cycle.

Among the obtained heterocyclic 1,4-naphthoquinone derivatives, potential fungicides, bactericides, plant growth regulators with higher activity and lower toxicity than ethanol were identified, structure-effect dependence for the synthesized compounds was established.

References


