

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

Iryna Buchkevych^{1,*}, Mariia Kurka¹, Anna Krvavych¹, Natalija Monka¹, Volodymyr Novikov¹, Vira Lubenets¹

¹ Department of Technology of Biologically Active Substances, Pharmacy & Biotechnology, Lviv National Polytechnic University, S. Bandery Str. 12, Lviv, Ukraine; irynabuchkevych@gmail.com (I.B), mariia.s.kurka@lpnu.ua (M.K.), anna.krv85@gmail.com (A.K.), mnatalija1985@gmail.com (N.M.), vira.i.lubenets@lpnu.ua (V.I);

* Correspondence: irynabuchkevych@gmail.com (I.B.);

Scopus Author ID 36124695600

Received: 18.01.2021; Revised: 20.02.2021; Accepted: 23.02.2021; Published: 1.03.2021

Abstract: As a result of the carried out research it was synthesized an order of new potentially biologically active modified N-,O-contained heterocycles on the base of amino acid derivatives of 2,6,7-nitrogen substituted-3-chloro-1,4-naphthoquinone. It was established that among synthesized compounds, there are potential antimicrobial substances with high activity.

Keywords: amino acid; imidazole; oxazole; naphthoquinone.

© 2021 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

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

2.1. General experimental details.

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-dihydronaphthalen-2-yl]-glycine (2a C₁₈H₁₈ClN₃O₆) ¹H NMR (400 MHz, DMSO-d₆) 9.73 (1H, s, NH); 8.53 (1H, s, CH_{ar}); 7.85 (1H, s, CH_{ar}); 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-dihydronaphthalen-2-yl]-glycine (2b C₂₁H₂₄ClN₃O₆S) ¹H NMR (400 MHz, DMSO-d₆) 9.71 (1H, s, NH); 8.52 (1H, s, CH_{ar}); 7.84 (1H, s, CH_{ar}); 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, ν_{max}/sm⁻¹) 3205 (NH); 1693,1650 (C=O);

N-[3-(acetylamino)-7-chloro-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydronaphthalen-2-yl]-glycine (2c C₂₅H₂₄ClN₃O₆) ¹H NMR (400 MHz, DMSO-d₆) 9.68 (1H, s, NH); 8.57 (1H, s, CH_{ar}); 7.84 (1H, s, CH_{ar}); 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, ν_{max}/sm⁻¹) 3215 (NH); 1685,1645(C=O);

N-[3-(acetylamino)-7-chloro-6-morpholin-4-yl-5,8-dioxo-5,8-dihydronaphthalen-2-yl]-methionine (2d C₁₉H₂₀ClN₃O₅) ¹H NMR (400 MHz, DMSO-d₆) 9.58 (1H, s, NH); 8.46 (1H, s, CH_{ar}); 8.02 (1H, d, CH_{ar}); 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, ν_{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-dihydronaphthalen-2-yl]-methionine (2e C₂₂H₂₆ClN₃O₅S) ¹H NMR (400 MHz, DMSO-d₆) 9.67(1H, s, NH); 8.44 (1H, s, CH_{ar}); 8.01 (1H, d, CH_{ar}); 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, ν_{max}/sm⁻¹) 3180 (NH); 1675, 1660 (C=O)

N-[3-(acetylamino)-7-chloro-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydronaphthalen-2-yl]-methionine (2f C₂₆H₂₆ClN₃O₅) ¹H NMR (400 MHz, DMSO-d₆) 9.78 (1H, s, NH); 8.49 (1H, s, CH_{ar}); 8.00 (1H, d, CH_{ar}); 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, ν_{max}/sm⁻¹) 3222 (NH); 1670, 1655(C=O);

N-[3-(acetylamino)-7-chloro-6-morpholin-4-yl-5,8-dioxo-5,8-dihydronaphthalen-2-yl]-phenylalanine (2g C₂₂H₃₀ClN₃O₅) ¹H NMR (400 MHz, DMSO-d₆) 9.86 (3H, s, NH, OH); 8.52 (1H, s, CH_{ar}); 7.85 (1H, d, CH_{ar}); 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, ν_{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-dihydronaphthalen-2-yl]-phenylalanine (2h C₂₅H₃₄ClN₃O₅S) ¹H NMR (400 MHz, DMSO-d₆) 9.85 (3H, s, NH, OH); 8.50 (1H, s, CH_{ar}); 7.86 (1H, d, CH_{ar}); 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, ν_{max}/sm⁻¹) 3232 (NH); 1695,1645 (C=O);

N-[3-(acetylamino)-7-chloro-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydronaphthalen-2-yl]-phenylalanine (2i C₂₉H₃₄ClN₃O₅) ¹H NMR (400 MHz, DMSO-d₆) 9.78 (3H, s, NH, OH);

8.55 (1H, s, CH_{ar}); 7.83 (1H, d, CH_{ar}); 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, $\nu_{\text{max}}/\text{sm}^{-1}$) 3240 (NH); 1680,1655 (C=O);

General procedure of synthesis (3 a-i): To the suspension (30 mmole) of acylamino-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 acetonitrile, 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 C₁₈H₁₆ClN₃O₅) ¹H NMR (400 MHz, DMSO-d₆) 9.22 (1H, s, CH_{ar}); 9.11 (1H, s, CH_{ar}); 8.50 (1H, s, OH); 4.89 (2H, s, CH₂); 3.70-3.62 (8H, m, CH₂); 2.63 (3H, s, CH₃); IR (KBr, $\nu_{\text{max}}/\text{sm}^{-1}$) 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 C₂₁H₂₂ClN₃O₅S) ¹H NMR (400 MHz, DMSO-d₆) 9.23 (1H, s, CH_{ar}); 9.10 (1H, s, CH_{ar}); 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, $\nu_{\text{max}}/\text{sm}^{-1}$) 3000-2500 (COOH), 1687, 1665(C=O);

([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 C₂₆H₂₆ClN₃O₅) ¹H NMR (400 MHz, DMSO-d₆) 9.21 (1H, s, CH_{ar}); 9.15 (1H, s, CH_{ar}); 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, $\nu_{\text{max}}/\text{sm}^{-1}$) 3000-2500 (COOH), 1674, 1658 (C=O);

(2-[7-chloro-2-methyl-6-morpholin-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl]-4-(metylthio)butanoic acid) (3d C₁₉H₁₈ClN₃O₄) ¹H NMR (400 MHz, DMSO-d₆) 9,46 (1H, s, OH); 9.38 (1H, s, CH_{apom}); 9.04 (1H, s, CH_{ar}); 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, $\nu_{\text{max}}/\text{sm}^{-1}$) 3000, 2500 (COOH) 1678, 1661 (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. ¹³C NMR (100 MHz,DMSO-d₆) δ = 179.21, 178.24, 176.78, 165.39, 147.49, 145.04, 144.14, 130.17, 129.31, 127.54, 114.45, 96.09, 67.23, 53.65, 49.82, 31.17, 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-(metylthio)butanoic acid) (3e C₂₂H₂₄ClN₃O₄S) ¹H NMR (400 MHz, DMSO-d₆) 9,46 (1H, s, OH); 9.38 (1H, s, CH_{ar}); 9.02 (1H, s, CH_{ar}); 5.33 (1H, t, CH); 3.40-3.32 (4H, m, CH₂); 2.67(3H, t, 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, $\nu_{\text{max}}/\text{sm}^{-1}$) 3000-2500 (COOH) 1675, 1654 (C=O);

(2-[7-chloro-2-methyl-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydro-1N-napht[2,3-d]imidazol-1-yl]-4-(metylthio)butanoic acid) (3f C₂₆H₂₄ClN₃O₄) ¹H NMR (400 MHz, DMSO-d₆) 9,46 (1H, s, OH); 9.38 (1H, s, CH_{ar}); 9.07 (1H, s, CH_{ar}); 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, $\nu_{\text{max}}/\text{sm}^{-1}$) 3000-2500 (COOH) 1672, 1663 (C=O);

(2-[7-chloro-2-methyl-6-morpholine-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl]-3-phenylpropanoic acid) (3g C₂₂H₂₆ClN₃O₄) ¹H NMR (400 MHz, DMSO-d₆) 9.27 (1H, s, OH); 9.23 (1H, s, CH_{ar}); 9.10 (1H, s, CH_{ar}); 7.46 (2H, d, CH_{ar}); 7.35 (2H, t, CH_{ar}); 7.16 (1H, t, CH_{ar}); 5.60-5.56 (1H, m, CH); 3.70-3.62 (8H, m, CH₂); 3.38-3.17 (2H, m, CH₂); 2.67 (3H, s, CH₃); IR (KBr, ν_{max}/sm^{-1}) 3000, 2500 (COOH) 1680, 1665 (C=O); ¹³C NMR (100 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 = 179.21, 178.24, 175.15, 157.39, 147.49, 146.42, 143.77, 136.93, 131.38, 129.36, 127.22, 126.76, 114.45, 95.72, 67.23, 54.56, 49.82, 35.46, 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]-3-phenylpropanoic acid) (3h C₂₅H₃₂ClN₃O₄S) ¹H NMR (400 MHz, DMSO-d₆) 9.29 (1H, s, OH); 9.23 (1H, s, CH_{ar}); 9.08 (1H, s, CH_{ar}); 7.46 (2H, t, CH_{ar}); 7.35 (2H, t, CH_{ar}); 7.16 (1H, t, CH_{ar}); 5.60-5.56 (1H, m, CH); 3.41-3.32 (4H, m, CH₂); 3.20-3.14 (2H, m, CH₂); 2.67 (3H, s, CH₃); 1.59-1.51 (6H, m, CH₂); IR (KBr, ν_{max}/sm^{-1}) 3000-2500 (COOH) 1690, 1668(C=O);

(2-[7-chloro-2-methyl-6-dibutylamino-4-yl-5,8-dioxo-5,8-dihydro-1N-naphto[2,3-d]imidazol-1-yl]-3-phenylpropanoic acid) (3i C₂₉H₃₂ClN₃O₄) ¹H NMR (400 MHz, DMSO-d₆) 9.28 (1H, s, OH); 9.23 (1H, s, CH_{ar}); 9.13 (1H, s, CH_{ar}); 7.45 (2H, t, CH_{ar}); 7.35 (2H, t, CH_{ar}); 7.15 (1H, t, CH_{ar}); 5.60-5.56 (1H, m, CH); 3.63 (4H, t, CH₂); 3.40-3.14 (2H, m, CH₂); 2.67 (3H, s, CH₃); 1.93-1.86 (4H, m, CH₂); 1.44-1.35 (4H, m, CH₂); 0.94 (6H, s, CH₃); IR (KBr, ν_{max}/sm^{-1}) 3000-2500 (COOH) 1686, 1660(C=O).

General procedure of synthesis (4 a-c): To the suspension (50 mmole) of acylamino-1,4-naphthoquinone (1 a-i) in 20ml of acetic anhydride it was added 1,2 ml of (0,64 g, 50 mmole) H₂SO₄ conc., maintained at 50-60°C during 5-7 h., reactionary mixture was chilled to the room temperature, the residue was crystallized from acetonitrile, yield 65-67%. All other compounds of this series were synthesized by following the above procedure.

(7-chloro-2-methyl-6-morpholin-4-yl-naphto[2,3-d][1,3]oxazol-5,8-dione) (4a C₁₆H₁₅ClN₂O₄) ¹H NMR (400 MHz, DMSO-d₆) 8.91 (1H, s, CH_{ar}); 8.73 (1H, s, CH_{ar}); 3.70-3.62 (8H, m, CH₂); 2.61 (3H, s, CH₃); IR (KBr, ν_{max}/sm^{-1}) 1650 (C=O);

(7-chloro-2-methyl-6-piperidin-4-yl-naphto[2,3-d][1,3]oxazol-5,8-dione) ¹³C NMR (100 MHz, DMSO-d₆) δ = 179.21, 178.45, 163.80, 151.35, 150.72, 147.49, 145.97, 130.47, 124.37, 114.45, 110.35, 14.30 ppm. (4b C₁₇H₁₇ClN₂O₃) ¹H NMR 8.91 (1H, s, CH_{ar}); 8.71 (1H, s, CH_{ar}); 3.40-3.32 (4H, m, CH₂); 2.61 (3H, s, CH₃); 1.59-1.51 (6H, m, CH₂); IR (KBr, ν_{max}/sm^{-1}) 1655 (C=O);

(7-chloro-2-methyl-6-dibutylamino-4-yl-naphto[2,3-d][1,3]oxazol-5,8-dione) (4c C₂₀H₂₇ClN₂O₃) ¹H NMR (400 MHz, DMSO-d₆) 8.93 (1H, s, CH_{ar}); 8.76 (1H, s, CH_{ar}); 3.63 (4H, t, CH₃); 2.61 (3H, s, CH₃); 1.93-1.86 (4H, m, CH₂); 1.44-1.36 (4H, m, CH₂); 0.94 (6H, t, CH₃); IR (KBr, ν_{max}/sm^{-1}) 1648 (C=O).

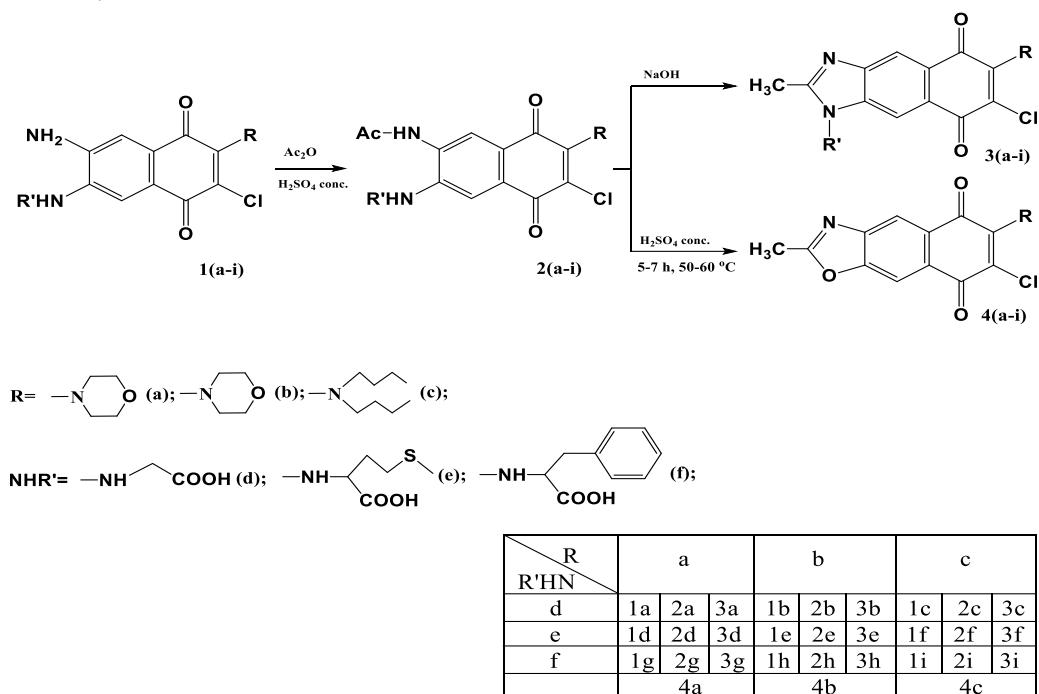
2.2. Biological studies.

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 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

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).



Scheme 1. Synthesis of imidazole and oxazole derivatives of 2,6,7-N-substituted-3-chloro-1,4-naphthoquinones.

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, CH_{ar}); 8,73 (1H, s, CH_{ar}); 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

Compound Microorganism	Diameter of inhibition zone, mm													
	3a	3b	3c	3d	3e	3.10f	3g	3h	3i	4a	4b	4c	DCNQ	Oxacillin
<i>E. coli</i>	0	0	0	0	0	0	0	0	0	27	16	17	15	0
<i>S. aureus</i>	18	20	17	20	19	17	18	17	16	26	22	24	18	24
<i>C. tenuis</i>	16	19	17	19	16	17	15	16	17	27	28	30	23	-

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

1. Ravichandiran, P.; Sheet, S.; Premnath, D.; Kim, A.R.; Yoo, D.J. 1,4-Naphthoquinone Analogues: Potent Antibacterial Agents and Mode of Action Evaluation. *Molecules* **2019**, *24*, <https://doi.org/10.3390/molecules24071437>.
2. Ravichandiran, P.; Maslyk, M.; Sheet, S.; Janeczko, M.; Premnath, D.; Kim, A.R.; Park, B.-H.; Han, M.-K.; Yoo, D.J. Synthesis and Antimicrobial Evaluation of 1,4-Naphthoquinone Derivatives as Potential Antibacterial Agents. *ChemistryOpen* **2019**, *8*, 589-600, <https://doi.org/10.1002/open.201900077>.
3. Lubenets, V.I.; Vasylyuk, S.V.; Goi, O.V.; Novikov, V.P. Reaction of 6,7-dichloroquinoline-5,8-quinone with thiosulfonic acid salts. *Chemistry of Heterocyclic Compounds* **2006**, *42*, 961-962, <https://doi.org/10.1007/s10593-006-0189-9>.

4. I. Buchkevych, M. Kurka, V. Chervetsova, A. Krvavych, N. Monka, V. Lubenets, V. Novikov. Synthesis of condensed nitrogen-containing heterocycles of substituted 1,4-naphthoquinone. *Voprosy khimii i khimicheskoi tekhnologii*, 2020, 1, 3-9, <http://dx.doi.org/10.32434/0321-4095-2020-128-1-3-9>
5. M. Janeczko, K. Kubiński, A. Martyna, A. Muzychka, A. Boguszewska-Czubara, S. Czernik, M. Tokarska-Rodak, M. Chwedczuk, O. Demchuk, H. Golczyk, M. Małyk. 1,4-Naphthoquinone derivatives potently suppress *Candida albicans* growth, inhibit formation of hyphae and show no toxicity toward zebrafish embryos. *Journal of Medical Microbiology* 2018, 67, 598–609. <https://doi.org/10.1099/jmm.0.0007>
6. Choudhari, D.; Salunke-Gawali, S.; Chakravarty, D.; Shaikh, S.R.; Lande, D.N.; Gejji, S.P.; Rao, P.K.; Satpute, S.; Puranik, V.G.; Gonnade, R. Synthesis and biological activity of imidazole based 1,4-naphthoquinones. *New J. Chem.* **2020**, 44, 6889-6901, <https://doi.org/10.1039/C9NJ04339J>.
7. Wellington, K.W.; Nyoka, N.B.P.; McGaw, L.J. Investigation of the antibacterial and antifungal activity of thiolated naphthoquinones. *Drug Dev. Res.* **2019**, 80, 386-394, <https://doi.org/10.1002/ddr.21512>.
8. Lubenets, V.; Karpenko, O.; Ponomarenko, M.; Zahoriy, G.; Krychkovska, A.; Novikov, V. Development of new antimicrobial compositions of thiosulfonate structure. *Chemistry & Chemical Technology* **2013**, <https://doi.org/10.23939/chcht07.02.119>.
9. Polish, N.V.; Marintsova, N.G.; Zhurakhivska, L.R.; Novikov, V.P.; Vovk, M.V. Synthesis and prediction of the biological activity of heterocyclic n-derivatives naphthoquinone. *Chemistry, Technology and Application of Substances* **2019**, 2, 69-75, <https://doi.org/10.23939/ctas2019.01.069>.
10. Vasylyuk, S.; Komarovska-Porokhnyavets, O.; Novikov, V.; Lubenets, V. Modification of alkyl esters of 4-aminobenzenethiosulfonic acid by S-triazine fragment and investigation of their growth-regulatory activity. *Chemistry & Chemical Technology* **2018**, 12, 24-28, <https://doi.org/10.23939/chcht12.01.024>.
11. Song, R.; Yu, B.; Friedrich, D.; Li, J.; Shen, H.; Krautscheid, H.; Huang, S.D.; Kim, M.-H. Naphthoquinone-derivative as a synthetic compound to overcome the antibiotic resistance of methicillin-resistant *S. aureus*. *Communications Biology* **2020**, 3, 529, <https://doi.org/10.1038/s42003-020-01261-0>.
12. Polish, N.; Voitsakhivska, O.; Marintsova, N.; Zhurakhivska, L.; Novikov, V.; Bohza, S. Primary screening of the biological activity of heterocyclic aminoderivatives of 2,3-dichloro-1,4-naphthoquinone. *ScienceRise: Pharmaceutical Science* **2019**, 10.15587/2519-4852.2019.188127, 37-42, <https://doi.org/10.15587/2519-4852.2019.188127>.
13. da Silva, A.J.M.; Netto, C.D.; Pacienza-Lima, W.; Torres-Santos, E.C.; Rossi-Bergmann, B.; Maurel, S.; Valentin, A.; Costa, P.R.R. Antitumoral, antileishmanial and antimalarial activity of pentacyclic 1, 4-naphthoquinone derivatives. *J. Braz. Chem. Soc.* **2009**, 20, 176-182, <https://doi.org/10.1590/S0103-50532009000100026>.
14. Ehrhardt, K.; Davioud-Charvet, E.; Ke, H.; Vaidya, A.B.; Lanzer, M.; Deponte, M. The Antimalarial Activities of Methylene Blue and the 1,4-Naphthoquinone 3-[4-(Trifluoromethyl)Benzyl]-Menadione Are Not Due to Inhibition of the Mitochondrial Electron Transport Chain. *Antimicrob. Agents Chemother.* **2013**, 57, 2114, <https://doi.org/10.1128/AAC.02248-12>.
15. Bolibrugh, K.; Polovkovych, S.; Khoumeri, O.; Halenova, T.; Nikolaeva, I.; Savchuk, O.; Terme, T.; Vanelle, P.; Lubenets, V.; Novikov, V. Synthesis and Anti-Platelet Activity of Thiosulfonate Derivatives Containing a Quinone Moiety. *Sci. Pharm.* **2015**, 83, <https://doi.org/10.3797/scipharm.1411-14>.
16. Monroy-Cárdenas, M.; Méndez, D.; Trostchansky, A.; Martínez-Cifuentes, M.; Araya-Maturana, R.; Fuentes, E. Synthesis and Biological Evaluation of Thio-Derivatives of 2-Hydroxy-1,4-Naphthoquinone (Lawsone) as Novel Antiplatelet Agents. *Frontiers in Chemistry* **2020**, 8, 533, <https://doi.org/10.3389/fchem.2020.00533>.
17. Oramas-Royo, S.; López-Rojas, P.; Amesty, Á.; Gutiérrez, D.; Flores, N.; Martín-Rodríguez, P.; Fernández-Pérez, L.; Estévez-Braun, A. Synthesis and Antiplasmoidal Activity of 1,2,3-Triazole-Naphthoquinone Conjugates. *Molecules* **2019**, 24, <https://doi.org/10.3390/molecules24213917>.
18. Delarmelina, M.; Daltoé, R.D.; Cerri, M.F.; Madeira, K.P.; Rangel, L.; Lacerda Júnior, V.; Romão, W.; Taranto, A.G.; Greco, S.J. Synthesis, antitumor activity and docking of 2, 3-(substituted)-1, 4-naphthoquinone derivatives containing nitrogen, oxygen and sulfur. *J. Braz. Chem. Soc.* **2015**, 26, 1804-1816, <https://doi.org/10.5935/0103-5053.20150157>.
19. Aminin, D.; Polonik, S. 1,4-Naphthoquinones: Some Biological Properties and Application. *Chem. Pharm. Bull.* **2020**, 68, 46-57, <https://doi.org/10.1248/cpb.c19-00911>.
20. Khraiwesh, M.H.; Lee, C.M.; Brandy, Y.; Akinboye, E.S.; Berhe, S.; Gittens, G.; Abbas, M.M.; Ampy, F.R.; Ashraf, M.; Bakare, O. Antitrypanosomal activities and cytotoxicity of some novel imidosubstituted 1,4-naphthoquinone derivatives. *Arch. Pharmacal Res.* **2012**, 35, 27-33, <https://doi.org/10.1007/s12272-012-0103-1>.
21. Shen, X.-b.; Wang, Y.; Han, X.-z.; Sheng, L.-q.; Wu, F.-f.; Liu, X. Design, synthesis and anticancer activity of naphthoquinone derivatives. *J. Enzyme Inhib. Med. Chem.* **2020**, 35, 773-785, <https://doi.org/10.1080/14756366.2020.1740693>.

22. Ravichandiran, P.; Subramaniyan, S.A.; Kim, S.-Y.; Kim, J.-S.; Park, B.-H.; Shim, K.S.; Yoo, D.J. Synthesis and Anticancer Evaluation of 1,4-Naphthoquinone Derivatives Containing a Phenylaminosulfanyl Moiety. *ChemMedChem* **2019**, *14*, 532-544, <https://doi.org/10.1002/cmdc.201800749>.
23. Jin, G.; Xiao, F.; Li, Z.; Qi, X.; Zhao, L.; Sun, X. Design, Synthesis, and Dual Evaluation of Quinoline and Quinolinium Iodide Salt Derivatives as Potential Anticancer and Antibacterial Agents. *ChemMedChem* **2020**, *15*, 600-609, <https://doi.org/10.1002/cmdc.202000002>.
24. Kacmaz, A.; Deniz, N.G.; Aydinli, S.G.; Sayil, C.; Onay-Ucar, E.; Mertoglu, E.; Arda, N. Synthesis and antiproliferative evaluation of some 1,4-naphthoquinone derivatives against human cervical cancer cells. *Open Chemistry* **2019**, *17*, 337-345, <https://doi.org/10.1515/chem-2019-0030>.
25. Ghosh, S.K.; Ganta, A.; Spanjaard, R.A. Discovery and cellular stress pathway analysis of 1,4-naphthoquinone derivatives with novel, highly potent broad-spectrum anticancer activity. *J. Biomed. Sci.* **2018**, *25*, 12, <https://doi.org/10.1186/s12929-018-0408-6>.
26. Yıldırım, H.; Bayrak, N.; Tuyun, A.F.; Kara, E.M.; Çelik, B.Ö.; Gupta, G.K. 2,3-Disubstituted-1,4-naphthoquinones containing an arylamine with trifluoromethyl group: synthesis, biological evaluation, and computational study. *RSC Advances* **2017**, *7*, 25753-25764, <https://doi.org/10.1039/C7RA00868F>.
27. Futuro, D.O.; Ferreira, P.G.; Nicoletti, C.D.; Borba-Santos, L.P.; Silva, F.C.; Rozental, S.; Ferreira, V.F. The antifungal activity of naphthoquinones: An integrative review. *An. Acad. Bras. Cienc.* **2018**, *90*, 1187-1214, <https://doi.org/10.1590/0001-3765201820170815>.
28. Arasoglu, T.; Mansuroglu, B.; Derman, S.; Gumus, B.; Kocyigit, B.; Acar, T.; Kocacaliskan, I. Enhancement of Antifungal Activity of Juglone (5-Hydroxy-1,4-naphthoquinone) Using a Poly(d,L-lactic-co-glycolic acid) (PLGA) Nanoparticle System. *J. Agric. Food Chem.* **2016**, *64*, 7087-7094, <https://doi.org/10.1021/acs.jafc.6b03309>.
29. Islam, A.K.M.M.; Widhalm, J.R. Agricultural Uses of Juglone: Opportunities and Challenges. *Agronomy* **2020**, *10*, <https://doi.org/10.3390/agronomy10101500>.
30. Sanz Sharley, D.D.; Williams, J.M.J. Acetic acid as a catalyst for the N-acylation of amines using esters as the acyl source. *Chem. Commun.* **2017**, *53*, 2020-2023, <https://doi.org/10.1039/C6CC09023K>.
31. C. Liana Allen; S. Davulcu; J. M. J. Williams. Catalytic Acylation of Amines with Aldehydes or Aldoximes. *Org. Lett.*, 2010, *12*(22), 5096–5099, <https://doi.org/10.1021/o1101978h>.
32. M. Balouiri; M. Sadiki; S. Koraichilbnsouda. Methods for in vitro evaluating antimicrobial activity: A review. *Journal of Pharmaceutical Analysis*, 2016, *6*(2), 71-79, <https://doi.org/10.1016/j.jpha.2015.11.005>.
33. Gideon, P.E.; Sugumar, R.; David, D.C. An in vitro study of antibacterial and antifungal activity of Cynodon dactylon. *National Journal of Physiology, Pharmacy and Pharmacology* **2017**, *7*, 381, <https://doi.org/10.5455/njPPP.2017.7.1131912122016>.
34. Scorzoni, L.; Benaducci, T.; Almeida, A.M.F.; Silva, D.H.S.; Bolzani, V.d.S.; Gianinni, M.J.S.M. The use of standard methodology for determination of antifungal activity of natural products against medical yeasts *Candida* sp and *Cryptococcus* sp. *Braz. J. Microbiol.* **2007**, *38*, 391-397, <https://doi.org/10.1590/S1517-83822007000300001>.
35. Cherif, O.; Masmoudi, F.; Allouche, F.; Chabchoub, F.; Trigui, M. Synthesis, antibacterial, and antifungal activities of new pyrimidinone derivatives. *Heterocycl. Commun.* **2015**, *21*, 191-194, <https://doi.org/10.1515/hc-2015-0066>.
36. Gholampour-Azizi, I.; Rouhi, S.; Yahyayi, F. In vitro antifungal activity of Cucumis melo on *Candida albicans*. *Zahedan Journal of Research in Medical Sciences* **2015**, *17*, <https://doi.org/10.17795/zjrms1019>.
37. Moghadasi, R.; Rostami, A.; Hemmati-Sarapardeh, A.; Motie, M. Application of Nanosilica for inhibition of fines migration during low salinity water injection: Experimental study, mechanistic understanding, and model development. *Fuel* **2019**, *242*, 846-862, <https://doi.org/10.1155/2014/186864>.