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Synthesis and biological evaluation of new amino derivatives of 1,4-naphthoquinone

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ABSTRACT

Synthesized ranks of new biologically active compounds by nucleophilic substitution of chlorine atom in the amino acid chloride derivatives of 1,4-naphthoquinone. All structures characterized with standard methods of chemical analysis and spectroscopic techniques. Experimental biological screening of synthesized compounds carried out. Among the newly synthesized compounds detected non-embryotoxic fungicides and bactericides, which does not cause oxidative stress.

Keywords: 1,4-naphthoquinone, amino acids, amides, lactams.

INTRODUCTION

The 1,4-naphthoquinone moiety is an important part of many biologically active natural substances. They are produced by bacteria, fungi and higher plants. Both natural quinones and their synthetic analogs have been shown to exhibit a variety of biological activities. Naphthoquinone derivatives are characterized by significant pharmacological properties - they are cytotoxic, they have significant antibacterial, antifungal, antiviral, insecticidal, anti-inflammatory, antioxidative, antipyretic properties [1].

Our work is devoted modification of well-known biologically active 1,4-naphthoquinones and exploration the biological activity of it`s derivatives.

As it was reported previously, 2-amino acid-3-chloro-1,4-naphthoquinones are biologically active compound, which have two active sites, that extends the possibilities for further modification with obtaining new potentially biologically active compounds [2].

Halides of carboxylic acids are strong electrophilic reagents, their electrophilic properties are caused by presence of a positive charge on the carbon atom of the carbonyl group. As a result of electron acceptor properties of the halogen atom on the carbon atom of the carbonyl group electron density is significantly reduced, therefore halogen anhydrides are stronger electrophilic reagents than the corresponding carboxylic acids [3].

The difficulties associated with obtaining amino acid chlorides, are primarily at eliminating conditions for those side effects, that occur with acidophilic groups during chlorination of the carboxyl groups [4, 5]. Chlorides of amino acids and their derivatives are used in organic synthesis as highly reactive intermediates for the introduction with some functional groups and various pharmacophores [6].

Heterociclyc compounds such as lactams usually obtained by cyclization aminocarboxyc acids or their derivatives. Heating in acidic condition of ϫ- and δ-amino acids exposed intramolecular cyclization as result of interaction between amino and carboxyl groups [7, 8]. Amino acids are often used for the synthesis of lactams, where the carboxyl group converted into a more reactive moiety such as ester [9].

Modification of 1,4-naphthoquinone and its derivatives causes undeniable interest, as these structures are considered to be leading in the synthesis and discovery of new classes of potentially biologically active compounds

EXPERIMENTAL SECTION

IR spectra were recorded with spectrophotometer Specord M-80 in KBr tablets. NMR spectra were recorded on spectrometer Varian VXR-300 and ^{1}H chemical shifts measured in relation with TMS internal standard in δ ppm. All melting points are uncorrected. Thin layer chromatography (TCL) was performed on Silufol UV-254 and visualized under UV or with iodine vapor. Elemental analysis of compounds was conducted in standard laboratory setting designed for microanalysis. The starting materials, auxiliary compounds and solvents used in this work were obtained commercially and purified if needed.

General method of synthesis of amino acid chloride derivatives of 1,4-naphthoquinon (5-7).

Synthesis of 4-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)amino]butanoyl chloride (7).
To (0,0033 mol) of 4-[3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)amino] butanoic acid (**3**) dissolved in 20 ml of dry methylene chloride added (0,0066 mol) of oxalyl chloride. The reaction was carried out at boiling using a calcium-chlorine tube. The progress of the reaction was monitored by TLC. The reaction time was – 1,5 hour. Then the solvent was removed under vacuum to obtain the product as a orange colored powder.

General method of synthesis of amide derivatives of 1,4-naphthoquinone (8-10 a-e).

Synthesis of 4-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)amino]-N-(propanyl-2) butanamide (10 c).
To (0.0032 mol) of 4-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)amino]butanoyl chloride (**7**) was dissolved in 30 ml of dry benzene then (0.0064 mol) of diethylamine. The reaction was performed without heating for 20 minutes. Then the reaction mixture was filtered to remove hydrochloric amine salt. The solvent was removed under vacuum and washed with hexane.

Red crystals product were obtained with yield of 56-75%.

2-Chloro-3-{[2-(morpholinyl-4)-2-oxoethyl]amino}naphthalene-1,4-dione (8a).
Yield: 69 %; mp. 151-154 ^{o}C; Anal. Calcd. for $C_{16}H_{15}ClN_2O_4$: C, 57.41; H, 4.52; Cl, 10.59; N, 8.37. Found: C, 57.54; H, 4.39; Cl, 10.66; N, 8.42; IR (KBr): ν (cm^{-1}) 3328, 2985, 2850, 1690, 1659, 1608, 1596, 1558, 1336, 1296, 1136, 820, 728, 680, 554; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 7.98 (2H, d., CH, Ar), 7.84 – 7.79 (2H, m., CH, Ar), 7.12 (1H, s., NH), 4.45 – 4.39 (2H, d., 1-CH_2), 3.95 – 3.90 (4H, t., 3, 5-CH_2), 3.20 – 3.14 (4H, t., 2, 6-CH_2).

2-Chloro-3-{[2-oxo-2-(piperidinyl-4)ethyl]amino}naphthalene-1,4-dione (8b).
Yield: 53 %; mp. 108-110 ^{o}C; Anal. Calcd. for $C_{17}H_{17}ClN_2O_3$: C, 61.36; H, 5.15; Cl, 10.65; N, 8.42. Found: C, 61.24; H, 5.22; Cl, 10.69; N, 8.48; IR (KBr): ν (cm^{-1}) 3328, 2938, 2856, 1690, 1636, 1600, 1576, 1508, 1456, 1328, 1296, 1136, 825, 720, 680, 545; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.04 – 8.00 (2H, d., CH, Ar), 7.80 – 7.74 (2H, m., CH, Ar), 7.04 (1H, s., NH), 4.41 – 4.39 (2H, d., 1-CH_2), 2.88 – 2.84 (4H, t., 2, 6-CH_2), 2.68 – 2.65 (2H, t., 2-CH_2), 1.64 – 1.57 (6H, m.,3, 4, 5-CH_2).

2-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N,N-diethylacetamide (8c).
Yield: 59 %; mp. 89-92 ^{o}C; Anal. Calcd. for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; Cl, 11.05; N, 8.73. Found: C, 59.85; H, 5.38; Cl, 11.13; N, 8.77; IR (KBr): ν (cm^{-1}) 3412, 2856, 1748, 1690, 1632, 1600, 1568, 1526, 1296, 1136, 824, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.02 – 7.97 (2H, d., CH, Ar), 7.89 – 7.78 (2H, m., CH, Ar), 7.68 (1H, s., NH), 3.48 – 3.45 (2H, d., 1-CH_2), 3.55 – 3.43 (4H, m., -CH_2), 2.63 – 2.56 (2H, t., 2-CH_2), 1.09 – 1.00 (6H, m.,-CH_3).

N-Butyl-2-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]acetamide (8d).
Yield: 71 %; mp. 133-136 ^{o}C; Anal. Calcd. for $C_{16}H_{17}ClN_2O_3$: C, 59.91; H, 5.34; Cl, 11.05; N, 8.73. Found: C, 59.94; H, 5.39; Cl, 11.01; N, 8.78; IR (KBr): ν (cm^{-1}) 3330, 2856, 1690, 1600, 1580, 1456 , 1344, 1088, 824, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.01 – 7.99 (2H, d., CH, Ar), 7.85 – 7.77 (2H, m., CH, Ar), 7.56 (1H, s., NH), 7.43 (1H, s., NH), 3.44 – 3.41 (2H, q., 1-CH_2), 3.58 – 3.49 (2H, q., 3-CH_2), 2.06 – 1.95 (4H, m., 4-CH_2), 1.45 – 1.37 (2H, m., 5-CH_2), 1.00 – 0.93 (3H, t., CH_3).

2-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-phenylacetamide (8e).
Yield: 58 %; mp. 147-150°C; Anal. Calcd. for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; Cl, 10.40; N, 8.22. Found: C, 63.68; H, 3.90; Cl, 10.37; N, 8.27; IR (KBr): ν (cm^{-1}) 3330, 2856, 1690, 1600, 1580, 1456, 1344, 1088, 824, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.01 – 7.99 (2H, d., CH, Ar), 7.85 – 7.77 (2H, m., CH, Ar), 7.56 (1H, s., NH), 7.43 (1H, s., NH), 3.44 – 3.41 (2H, q., 1-CH_2), 3.58 – 3.49 (2H, q., 3-CH_2), 2.06 – 1.95 (4H, m., 4-CH_2), 1.45 – 1.37 (2H, m., 5-CH_2), 1.00 – 0.93 (3H, t., CH_3).

2-Chloro-3-{[3-(morpholinyl-4)-3-oxopropyl]amino}naphthalene-1,4-dione (9a).
Yield: 72 %; mp. 134-137 °C; Anal. Calcd. for $C_{17}H_{17}ClN_2O_4$: C, 58.54; H, 4.91; Cl, 10.16; N, 8.03. Found: C, 58.33; H, 4.94; Cl, 10.11; N, 8.10; IR (KBr): ν (cm^{-1}) 3280, 2984, 2856, 1680, 1640, 1604, 1576, 1448, 1336, 1296, 1248, 1136, 1104, 824, 728, 680, 552; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 7.98 (2H, d., CH, Ar), 7.74 – 7.58 (2H, m., CH, Ar), 7.04 (1H, s., NH), 4.15 – 4.09 (2H, q., 1-CH_2), 3.95 – 3.90 (4H, t., 3, 5-CH_2), 3.17 – 3.10 (4H, t., 2, 6-CH_2), 2.64 – 2.56 (2H, t., 2-CH_2).

2-Chloro-3-{[3-oxo-3-(piperidinyl-4)propyl]amino}naphthalene-1,4-dione (9b).
Yield: 64 %; mp. 98-100 °C; Anal. Calcd. for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; Cl, 10.22; N, 8.08. Found: C, 62.45; H, 5.28; Cl, 10.18; N, 8.41 IR (KBr): ν (cm^{-1}) 3336, 2936, 2856, 1680, 1636, 1608, 1576, 1508, 1452, 1328, 1296, 1252, 1224, 1136, 1016, 816, 720, 680, 546; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.06 – 8.00 (2H, d., CH, Ar), 7.78 – 7.64 (2H, m., CH, Ar), 7.09 (1H, s., NH), 4.28 – 4.21 (2H, q., 1-CH_2), 2.88 – 2.80 (4H, t., 2, 6-CH_2), 2.68 – 2.62 (2H, t., 2-CH_2), 1.64 – 1.57 (6H, m.,3, 4, 5-CH_2).

3-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N,N-diethylpropanamide (9c).
Yield: 57 %; mp. 68-70 °C; Anal. Calcd. for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; Cl, 10.59; N, 8.37. Found: C, 60.98; H, 5.68; Cl, 10.53; N, 8.43; IR (KBr): ν (cm^{-1}) 3459, 3412, 2856, 1728, 1680, 1632, 1600, 1568, 1528,1323, 1296, 1136, 828, 724, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 7.96 (2H, d., CH, Ar), 7.89 – 7.79 (2H, m., CH, Ar), 7.56 (1H, s., NH), 3.98 – 3.91 (2H, q., 1-CH_2), 3.55 – 3.43 (4H, m., -CH_2), 2.61 – 2.54 (2H, t., 2-CH_2), 1.16 – 1.09 (6H, m.,-CH_3).

N-Butyl-3-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]propanamide (9d).
Yield: 71 %; mp. 117-120°C; Anal. Calcd. for $C_{17}H_{19}ClN_2O_3$: C, 60.99; H, 5.72; Cl, 10.59; N, 8.37. Found: C, 61.22; H, 5.68; Cl, 10.55; N, 8.44; IR (KBr): ν (cm^{-1}) 3430, 3336, 2854, 1690, 1600, 1580, 1456, 1344, 1088, 824, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.02 – 7.99 (2H, d., CH, Ar), 7.86 – 7.76 (2H, m., CH, Ar), 7.63 (1H, s., NH), 7.53 (1H, s., NH), 3.98 – 3.91 (2H, q., 1-CH_2), 3.58 – 3.49 (2H, q., 4-CH_2), 2.63 – 2.56 (2H, t., 2-CH_2), 2.01 – 1.94 (4H, m., 5-CH_2), 1.45 – 1.37 (2H, m., 6-CH_2), 1.00 – 0.93 (3H, t., CH_3).

3-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-phenylpropanamide (9e).
Yield: 65 %; mp. 132-134 °C; Anal. Calcd. for $C_{19}H_{15}ClN_2O_3$: C, 64.32; H, 4.26; Cl, 9.99; N, 7.90. Found: C, 64.36; H, 4.31; Cl, 9.78; N, 7.95; IR (KBr): ν (cm^{-1}) 3272, 3050, 1752, 1680, 1592, 1504, 1344, 1288, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 9.39 (1H, s., NH), 8.00 – 7.94 (2H, dd., CH, Ar), 7.86 – 7.73 (2H, m., CH, Ar), 7.42 (1H, s., NH), 7.30 – 7.20 (2H, t., 3, 5-CH, Ar), 7.16 – 7.07 (1H, t., 4-CH, Ar), 7.13 – 7.10 (2H, d., 2, 6-CH, Ar), 3.87 – 3.75 (2H, q., 1-CH_2), 2.34 – 2.25 (2H, t., 2-CH_2).

2-Chloro-3-{[4-(morpholinyl-4)-4-oxobutyl]amino}naphthalene-1,4-dione (10a).
Yield: 73 %; mp. 120-122 °C; Anal. Calcd. for $C_{18}H_{19}ClN_2O_4$: C, 59.59; H, 5.28; Cl, 9.77; N, 7.72. Found: C, 59.22; H, 4.89; Cl, 9.57; N, 7.80; IR (KBr): ν (cm^{-1}) 3424, 2864, 2312, 1704, 1676, 1632, 1592, 1564, 1416, 1336, 1256, 1112, 984, 964, 728, 680, 552; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.03 – 7.99 (2H, d., CH, Ar), 7.78 – 7.68 (2H, m., CH, Ar), 7.22 (1H, s., NH), 4.22 – 4.15 (2H, q., 1-CH_2), 3.89 – 3.96 (4H, t., 3, 5-CH_2), 3.19 – 3.11 (4H, t., 2, 6-CH_2), 2.34 – 2.20 (2H, t., 2-CH_2), 2.35 – 2.22 (2H, t., 3-CH_2), 1.85 – 1.78 (4H, m., 2-CH_2).

2-Chloro-3-{[4-oxo-4-(piperidinyl-1)butyl]amino}naphthalene-1,4-dione (10b).
Yield: 67 %; mp. 81-82 °C; Anal. Calcd. for $C_{19}H_{21}ClN_2O_3$: C, 63.24; H, 5.87; Cl, 9.83; N, 7.76. Found: C, 63.35; H, 5.64; Cl, 9.75; N, 7.80 IR (KBr): ν (cm^{-1}) 3308, 2936, 2836, 1734, 1680, 1640, 1600, 1456 1336, 1256, 728, 680, 544; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.05 – 8.00 (2H, d., CH, Ar), 7.79 - 7.63 (2H, m., CH, Ar), 7.10 (1H, s., NH), 4.20 – 4.31 (2H, q., 1-CH_2), 2.85 – 2.78 (4H, t., 2, 6-CH_2), 2.35 – 2.27 (2H, t., 3-CH_2), 1.89 – 1.80 (4H, m., 2-CH_2), 1.65 – 1.54 (6H, m., 3, 4, 5-CH_2).

4-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N,N-diethylbutanamide (10c).
Yield: 68 %; mp. 74-75°C; Anal. Calcd. for $C_{18}H_{21}ClN_2O_3$: C, 61.99; H, 6.07; Cl, 10.16; N, 8.03. Found: C, 61.98; H, 6.08; Cl, 10.14; N, 8.12; IR (KBr): ν (cm^{-1}) 3410, 3336, 2856, 1738, 1682, 1633, 1609, 1568, 1520,1444, 1328, 1296, 1136, 1029, 824, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 7.96 (2H, d., CH, Ar), 7.87 – 7.72 (2H, m.,

CH, Ar), 7.39 (1H, s., NH), 3.90 – 3.84 (2H, q., 1-CH_2), 3.30 – 3.25 (4H, m., -CH_2), 2.33 – 2.22 (2H, t., 3-CH_2), 1.78 – 1.69 (2H, m., 2-CH_2), 1.19 – 1.10 (3H, t., -CH_3), 1.08 – 0.99 (3H, t., -CH_3).

N-Butyl-4-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]butanamide (10d).
Yield: 69 %; mp. 109-110 ^oC; Anal. Calcd. for $C_{18}H_{21}ClN_2O_3$: C, 61.99; H, 6.07; Cl, 10.16; N, 8.03. Found: C, 61.94; H, 6.13; Cl, 9.92; N, 8.10; IR (KBr): ν (cm^{-1}) 3280, 3276, 2864, 1696, 1608, 1576, 1456 , 1340, 1296, 1088, 824, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 8.98 (2H, d., CH, Ar), 7.84 – 7.66 (2H, m., CH, Ar), 7.52 (1H, s., NH), 7.41 (1H, s., NH), 3.90 – 3.84 (2H, q., 1-CH_2), 3.52 – 3.41 (2H, q., 5-CH_2), 2.33 – 2.26 (2H, t., 3-CH_2), 1.87 – 1.80 (4H, m., 2, 6-CH_2), 1.30 – 1.22 (2H, m., 7-CH_2), 0.92 – 0.80 (3H, t., CH_3).

4-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-phenylbutanamide (10e).
Yield: 72 %; mp. 116-118 ^oC; Anal. Calcd. for $C_{19}H_{15}ClN_2O_3$: C, 65.13; H, 4.65; Cl, 9.61; N, 7.60. Found: C, 65.43; H, 4.68; Cl, 9.72; N, 7.77; IR (KBr): ν (cm^{-1}) 3272, 3050, 1752, 1680, 1592, 1504, 1344, 1288, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 9.39 (1H, s., NH), 8.00 – 7.94 (2H, d.d., CH, Ar), 7.86 – 7.73 (2H, m., CH, Ar), 7.42 (1H, s., NH), 7.30 – 7.20 (2H, t., 3, 5-CH, Ar), 7.16 – 7.07 (1H, t., 4-CH, Ar), 7.13 – 7.10 (2H, d., 2, 6-CH, Ar), 3.87 – 3.79 (2H, q., 1-CH_2), 2.34 – 2.25 (2H, t., 3-CH_2), 1.80 – 1.71 (2H, m., 2-CH_2).

General method of synthesis of amide derivatives of 1,4-naphthoquinone (8-10 f-h).

Synthesis of 4-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)amino]-N-(pyperidinyl-2)butanamide (10 e).
To (0.0032 mol) of 4-[(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)amino]butanoyl chloride (**7**) dissolved in 30 ml of dry acetone added (0.0025 mol) 2-aminopyridine. Pyridine was used as a catalyst. The progress of the reaction monitored by TLC. The reaction performed by heating (50^0C) for 2 hours. After the interaction the solvent evaporated, and precipitated product was washed with a 2% aqueous solution of K_2CO_3. The product was recrystallized from petroleum ether.

Dark red crystals were obtained. Yields 53-68%.

2-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(pyridinyl-2)acetamide (8f).
Yield: 58 %; mp. 129-132 ^oC; Anal. Calcd. for $C_{17}H_{12}ClN_3O_3$: C, 59.75; H, 3.54; Cl, 10.37; N, 12.30. Found: C, 59.72; H, 3.57; Cl, 10.28; N, 12.41; IR (KBr): ν (cm^{-1}) 3450, 3308, 1725, 1690, 1640, 1600, 1580, 1568, 1296, 1029, 824, 733, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.07 – 8.05 (1H, d., 6-CH, Ar), 7.99 – 7.96 (2H, m., CH, Ar), 7.90 - 7.77 (2H, m., CH, Ar), 7.65 (1H, s., NH), 7.55 (1H, s., NH), 7.35 – 7.27 (1H, t., 5-CH, Ar), 7.13 – 7.10 (1H, d., 3-CH, Ar), 7.00 – 6.90 (1H, t., 4-CH, Ar), 4.44 – 4.41 (2H, d., 1-CH_2).

2-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(naphthalenyl-2) acetamide (8g).
Yield: 52 %; mp. 154-157 ^oC; Anal. Calcd. for $C_{22}H_{15}ClN_2O_3$: C, 67.61; H, 3.87; Cl, 9.07; N, 7.17. Found: C, 67.65; H, 7.19; Cl, 9.00; N, 7.23; IR (KBr): ν (cm^{-1}) 3305, 3004, 1716, 1690, 1635, 1604, 1586, 1568, 1520, 1488, 1135, 824, 733, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 7.97 (4H, d., 8-CH, Ar), 7.88 – 7.85 (1H, d., 4-CH, Ar), 7.78 – 7.66 (4H, m., 6, 7-CH, Ar), 7.65 – 7.58 (1H, d., 2-CH, Ar), 7.33 (1H, s., NH), 7.41 – 7.30 (1H, t., 3-CH, Ar), 7.20 (1H, s., NH), 3.45 – 3.42 (2H, d., 1-CH_2).

2-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(*9H*-carbazolyl-2) acetamide (8h).
Yield: 57 %; mp. 158-160 ^oC; Anal. Calcd. for $C_{24}H_{15}ClN_2O_3$: C, 69.49; H, 3.64; Cl, 8.55; N, 6.75. Found: C, 69.38; H, 6.68; Cl, 8.55; N, 6.84; IR (KBr): ν (cm^{-1}) 3333, 3079, 3009, 1729, 1680, 1600, 1572, 1452, 1176, 733, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.12 – 8.08 (4H, d., 1, 4, 5, 8-CH, Ar), 8.03 – 7.99 (2H, d., CH, Ar), 7.72 – 7.64 (2H, m., CH, Ar), 7.60 – 7.53 (4H, t., 2, 3, 6, 7-CH, Ar), 7.16 (1H, s., NH), 3.40 – 3.38 (2H, d., 1-CH_2).

3-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(pyridinyl-2) propanamide (9f).
Yield: 63 %; mp. 138-140 ^oC; Anal. Calcd. for $C_{18}H_{14}ClN_3O_3$: C, 60.77; H, 3.97; Cl, 9.96; N, 11.81. Found: C, 59.72; H, 3.57; Cl, 10.28; N, 12.41; IR (KBr): ν (cm^{-1}) 3448, 3288, 1710, 1689, 1635, 1610, 1580, 1568, 1526, 1440, 1336, 1296, 1136, 1029, 824, 735, 724, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.07 – 8.05 (1H, d., 6-CH, Ar), 7.98 – 7.96 (2H, d., CH, Ar), 7.94-7.86 (2H, m., CH, Ar), 7.68 (1H, s., NH), 7.55 (1H, s., NH), 7.33 – 7.25 (1H, t., 5-CH, Ar), 7.21 – 7.18 (1H, d., 3-CH, Ar), 7.11 – 7.04 (1H, t., 4-CH, Ar), 3.88 – 3.76 (2H, q., 1-CH_2), 2.33 – 2.25 (2H, t., 2-CH_2).

3-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(naphthalenyl-2) propanamide (9g).
Yield: 66 %; mp. 158-160 ^oC; Anal. Calcd. for $C_{23}H_{17}ClN_2O_3$: C, 68.24; H, 4.23; Cl, 8.76; N, 6.92. Found: C, 68.29; H, 4.30; Cl, 8.82; N, 6.99; IR (KBr): ν (cm^{-1}) 3405, 3304, 1723, 1690, 1640, 1600, 1586, 1568, 1520, 1488, 1250, 1135, 1029, 824, 733, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.00 – 7.97 (4H, d., 8-CH, Ar), 7.85 – 7.83 (1H, d., 4-

CH, Ar), 7.78 – 7.65 (4H, m., 6, 7-CH, Ar), 7.63 – 7.56 (1H, d., 2-CH, Ar), 7.53 (1H, s., NH), 7.41 – 7.30 (1H, t., 3-CH, Ar), 7.25 (1H, s., NH), 3.95 – 3.87 (2H, q., 1-CH_2), 2.38 – 2.27 (2H, t., 2-CH_2).

3-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(*9H*-carbazolyl-2) propanamide (9h).
Yield: 54 %; mp. 154-157 ^oC; Anal. Calcd. for $C_{25}H_{17}ClN_2O_3$: C, 70.01; H, 4.06; Cl, 6.35; N, 8,27. Found: C, 70.04; H, 4.01; Cl, 6.40; N, 8.33; IR (KBr): ν (cm^{-1}) 3308, 3088, 3004, 1735, 1680, 1600, 1572, 1452, 1176, 1088, 752, 724, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.16 – 8.05 (4H, m., 1, 4, 5, 8-CH, Ar), 8.05 – 7.99 (2H, d., CH, Ar), 7.70 – 7.60 (2H, m., CH, Ar), 7.57 – 7.43 (4H, t., 2, 3, 6, 7-CH, Ar), 7.03 (1H, s., NH), 3.90 – 3.83 (2H, q., 1-CH_2), 2.35 – 2.29 (2H, t., 2-CH_2).

4-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(pyridinyl-2) butanamide (10f).
Yield: 56 %; mp. 132-134 ^oC; Anal. Calcd. for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; Cl, 9.59; N, 11.36. Found: C, 61.86; H, 4.53; Cl, 9.91; N, 11.44; IR (KBr): ν (cm^{-1}), 3336, 3198, 1718, 1690, 1640, 1610, 1580, 1568, 1520,1446, 1329, 1296, 1255, 1136, 1029, 824, 738, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.09 – 8.05 (1H, d., 6-CH, Ar), 7.99 - 7.96 (2H, d., CH, Ar), 7.90 - 7.81 (2H, m., CH, Ar), 7.55 (1H, s., NH), 7.43 (1H, s., NH), 7.38 – 7.29 (1H, t., 5-CH, Ar), 7.17 – 7.10 (1H, d., 3-CH, Ar), 7.02 – 6.99 (1H, t., 4-CH, Ar), 3.74 – 3.65 (2H, q., 1-CH_2), 2.30– 2.21 (2H, t., 3-CH_2), 1.88 – 1.79 (2H, m., 2-CH_2).

4-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(naphthalenyl-2) butanamide (10g).
Yield: 53 %; mp. 142-145 ^oC; Anal. Calcd. for $C_{24}H_{19}ClN_2O_3$: C, 68.82; H, 4.57; Cl, 8.46; N, 6.69. Found: C, 68.76; H, 4.43; Cl, 8.35; N, 6.77; IR (KBr): ν (cm^{-1}) 3425, 3304, 1720, 1690, 1640, 1610, 1586, 1568, 1520,1480, 1350, 1280, 1258, 1136, 1029, 824, 733, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.05 – 7.92 (4H, d., 8-CH, Ar), 7.75 – 7.73 (1H, d., 4-CH, Ar), 7.68 – 7.52 (4H, m., 6, 7-CH, Ar), 7.48 – 7.46 (1H, d., 2-CH, Ar), 7.41 – 7.35 (1H, t., 3-CH, Ar), 7.50 (1H, s., NH), 7.39 (1H, s., NH), 3.93 – 3.87 (2H, q., 1-CH_2), 2.35 – 2.28 (2H, t., 3-CH_2), 1.86 – 1.79 (2H, m., 2-CH_2).

4-[(3-Chloro-1,4-dioxo-1,4-dihydronaphthalenenyl-2)amino]-N-(*9H*-carbazolyl-2) butanamide (10h).
Yield: 51 %; mp. 165-167 ^oC; Anal. Calcd. for $C_{26}H_{19}ClN_2O_3$: C, 70.51; H, 4.32; Cl, 8.00; N, 6.32. Found: C, 70.49; H, 4.38; Cl, 7.98; N, 6.37; IR (KBr): ν (cm^{-1}) 3305, 3080, 3008, 1735, 1680, 1600, 1572, 1452, 1232, 1176, 1088, 752, 724, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.10 – 8.05 (4H, d., 1, 4, 5, 8-CH, Ar), 8.03 – 7.95 (2H, d., CH, Ar), 7.70 – 7.60 (2H, m., CH, Ar), 7.41 – 7.33 (4H, t., 2, 3, 6, 7-CH, Ar), 6.85 (1H, s., NH), 3.90 – 3.78 (2H, q., 1-CH_2), 2.35 – 2.27 (2H, t., 3-CH_2), 1.85 – 1.77 (2H, m., 2-CH_2).

Synthesis of 1,4-bis(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2) piperazine-2,5-dione (12).
To suspension of (0.0038 mol) of [3-chloro-1,4-dixo-1,4- dihydronaphthalenyl-2)amino] acetic acid (**2**) in 20 ml dry toluene (0.015 mol) of thionyl chloride (**11**) was added. The reaction performed at heating (40^0C) using calcium-chlorine tube for 1,5 hour. Then catalytic amount of pyridine (2 dr.) was added into the reaction mixture and boiled for 5 hours. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the precipitate product was filtered, washed with a water and dried. Dark drown crystals were obtained with 42% yield.

1,4-Bis(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)piperazine-2,5-dione (12).
Mp. 123-126 ^oC; Anal. Calcd. for $C_{24}H_{12}N_2O_6Cl_2$: C, 58.20; H, 2.44; Cl, 14.32; N, 5.66. Found: C, 58.17; H, 2.43; Cl, 14.31; N, 5.79; IR (KBr): ν (cm^{-1}) 1808, 1768, 1744, 1696, 1680, 1632, 1616, 1568, 1512, 1472, 1416, 1388, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.12 (4H, d.,CH, Ar); 7.86 – 7.79 (4H, m., CH, Ar); 4.40 – 4.38 (4H, d., CH_2).

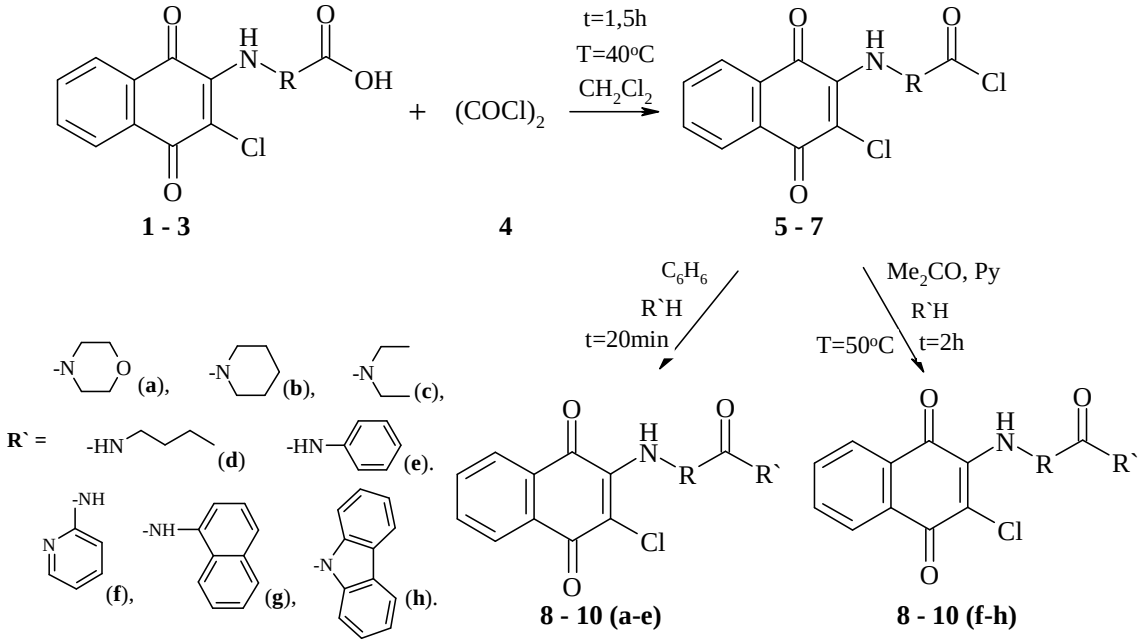
Synthesis of 2-choro-3-(2-oxoporrolidinyl-1)-naphthalene-1,4-dione (13).
To suspension of (0.0033 mol) of 4-[3-chloro-1,4-dioxo-1,4-naphthalenyl-2)amino] butanoic acid (**3**) in 20 ml dry chloroform added (0.01 mol) thionyl chloride (**11**). The reaction was performed at heating (40^0C) using calcium-chlorine tube for 1,5 hour. Then the reaction mixture was boiled for half an hour. The progress of the reaction was monitored by TLC. Upon completion of the reaction chloroform, tionil chloride and hydrogen chloride were removed under vacuum and dry residue washed with a little amount of water and then dried. Dark yellow crystals were received with yield of 93%.

2-Choro-3-(2-oxoporrolidinyl-1)-naphthalene-1,4-dione (13).
Mp. 123-126 ^oC; Anal. Calcd. for $C_{14}H_{10}NO_3Cl$: C, 60.99; H, 3.66; Cl, 12.86; N, 5.08. Found: C, 60.95; H, 3.59; Cl, 12.90; N, 5.16; IR (KBr): ν (cm^{-1}) 1712, 1672, 1600, 1552, 1400, 1328, 1268, 1144, 872, 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 7.99 – 7.94(2H, d., CH, Ar); 7.86 – 7.70 (2H, m., CH, Ar); 3.47 – 3.42 (2H, t., 1-CH_2), 2.41 – 2.36 (2H, t., 3-CH_2), 2.16 – 2.06 (2H, m., 2-CH_2).

RESULTS AND DISCUSSION

The amino acid derivatives of 1,4-naphthoquinone (**1-3**), with aliphatic amino acids which do not contain side chains, were chosen for the synthesis of chlorides, thus was reduced the probability of occurrence of side reactions due to the fewer number of reaction centers in the amino acid derivatives of 1,4-naphthoquinone (**1-3**) molecules. Accordingly, for the synthesis of a number of amino acid derivatives of 1,4-naphthoquinone (**1-3**) by the method described previously [2] the following amino acids: α-aminoacetic, β-aminopropanoic and ɤ-aminobutyric acids were selected.

Chlorination of amino acid derivatives of 1,4-naphthoquinone (**1-3**) were carried out by oxalyl chloride (**4**) is known as more soft and selective chlorinating agent in comparison with thionyl chloride (**11**) [10]. A synthesis of amino acid chloride derivatives of 1,4-naphthoquinone (**5-7**) were carried out in methylene chloride at temperature – 40^{o}C without the use of catalysts [11]. Amino acid chloride derivatives of 1,4-naphthoquinone (**5-7**) were obtained with high yield.

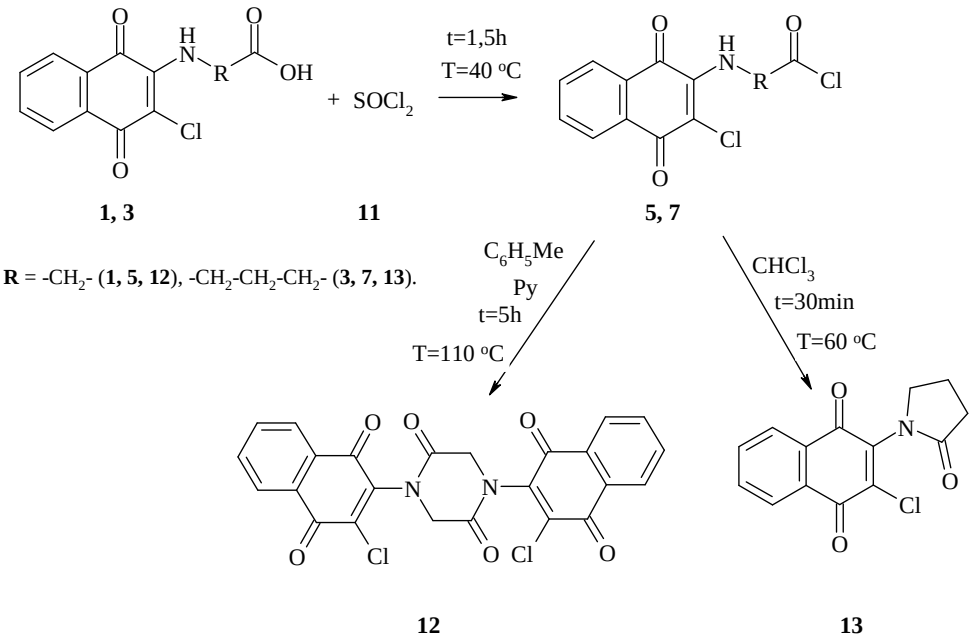


R = -CH_2- (**1, 5, 8**), -CH_2-CH_2- (**2, 6, 9**), -CH_2-CH_2-CH_2- (**3, 7, 10**).

Scheme 1

Amide derivatives of 1,4-naphthoquinone (**8-10 a-h**) were obtained by interaction of amino acid chloride derivatives of 1,4-naphthoquinone (**5-7**) with amines in mild condition. The desired structures (**8-10 a-h**) were obtained with high yields (53-75%).

Lactam substituted 1,4-naphthoquinones (**12-13**) were obtained by cyclization of amino acid chloride derivatives of 1,4-naphthoquinone (**5**, **7**). In this synthesis thionyl chloride (**11**) were used to obtain amino acid chloride derivatives of 1,4-naphthoquinone (**5**, **7**), as it is more rigid chlorinating agent, and therefore provides a more acidic conditions [10] which are necessary for N-acylation. For synthesis of lactam derivatives of 1,4-naphthoquinone (**12-13**), the reaction mixture was heated with or without a catalyst (pyridin).



Scheme 2

2-Chloro-3-(2-oxopyrrolidinyl-1)-[1,4]-naphthoquinone (**13**) was obtained as a result of intramolecular interaction, and 1,4-bis(3-chloro-1,4-dioxo-1,4-dihydronaphthalenyl-2)piperazine-2,5-dione (**12**) as a result of intermolecular interaction.

SPECTRAL DATA (analysis)

The IR spectra two pairs of peaks at 1680 and 1640 cm^{-1} (C=O) and 1600 and 1560cm^{-1} (C=C) belong to naphthoquinone rings. The bond at 3400-3100 cm^{-1} is due to valence vibration, and the band at 1520 cm^{-1} represents deformational vibrations of secondary amino groups of amide derivatives of 1,4-naphthoquinone (**8-10 a-h**). Presentes of (C–Cl) bond in amide and lactam derivatives of 1,4-naphthoquinone (**8-10 a-h**, **12-13**) were proved absorption at 680 cm^{-1} [12].

In the ^{1}H NMR spectra both duplet and triplet stretched within 8.00 – 7.80 ppm attributed to naphthoquinone fragments for all compounds (**8-10 a-h**, **12-13**). Protons of secondary amino groups were presented by broad singlet at 7.60 – 7.30 ppm, hydrogens of (CH_2) group of the amino acid carbon chain are shown in the range of 4.41 to 1.81 ppm.

NMR spectra of lactam derivatives of 1,4-naphthoquinone (**12-13**) weren`t contain signals of amino and carboxyl groups hydrogens in areas 7.60 – 7.30 and 12.90 – 12.10 ppm [13].

BIOLOGICAL ACTIVITY

Fungicidal and antibacterial activity of 2-amino acid-3-chloro-1,4-naphthoquinones (**1-3**) and their derivatives (**8-10 a-h**), (**12-13**) were tested on agar embedded cultures of the following bacteria *Escherichia coli, Staphylococcus aureus, Mycobacterium luteum* and fungi *Candida tenuis, Aspergillus niger* by using standard method [14]. It was found that all tested substances possess moderate antibacterial activity against gram-positive bacteria *S. aureus, M. luteum.* The culture of gram-negative bacteria *E. coli* proved resistance against all tested compounds. Lactam derivatives of 1,4-naphthoquinone (**12-13**) showed a strong effect on yeasts *C. tenuis* and fungi *A. niger*.

Among a number of the compounds revealed that structures (**1**), (**3**), (**8a**), (**9b**) and (**10d**) show antioxidant effect on cell proteins and fats. Also established that rest of substances do not cause oxidative stress.

Found that the amide derivatives of 1,4-naphthoquinone (**9a** and **9b**) at concentration 10^{-6}-10^{-9}M doesn`t show embryotoxic properties, embryos and larvae of loach *Misgurnus fossilis L*. developed normally and hatching process was equal control.

According to the experimental biological screening newly synthesized amide and lactam derivatives of 1,4-naphthoquinone are biologically active substances with wide range of action.

CONCLUSION

To conclude the series of new amino derivatives of 1,4-naphthoquinone synthesized with a relatively high yields using simple procedures and low costs time. Experimental biological screening determined ability of amino derivatives of 1,4-naphthoquinone inhibit the development and growth of bacterial and fungal cells and also their antioxidant properties and non-embryotoxicity were discovered.

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