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Research Article

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Synthesis and characteristics of amino acid derivatives of 1,4-naphthoquinone

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ABSTRACT

Synthesis optimization of a series of 2-amino acid-3-chloro-1,4-naphthoquinones demonstrated feasibility to conduct reactions in mild conditions providing relatively high yields, simple procedure and low time costs. Compounds were characterized with standard methods of chemical analysis and spectroscopic techniques. Physicochemical parameters of weight loss and start melting point were determined. Preliminary screening of synthesized compounds carried out with online based algorithm of prediction of activity spectra for synthesized substances (PASS).

Keywords: 1,4-naphthoquinone, 2,3-dichloro-1,4-naphthoquinone, amino acids.

INTRODUCTION

A large number of research papers dedicated to quinones and naphthoquinones [1-5]. N-derivatives of 1,4-naphthoquinone are widely studied and described, but still remains a significant area of unknown amino acid derivatives of 1,4-naphthoquinone. It is significant interest from a synthetic point of view, because of free, reactive capable carboxyl group of amino acid derivatives of 1,4-naphthoquinone, which can be used as base, for the synthesis of new biologically active compounds. Only series of esters [6] and amides [7] of amino acid derivatives of 1,4-naphthoquinone were obtained by conjunction of 1,4-naphthoquinone fragment and amino acid residues.

Recently, many studies have shown that naphthoquinone derivatives with substituted chlorine atom exhibit some activity against fungi [8]. And accordingly, as is well known, 2,3-dichloro-1,4-naphthoquinone and its derivatives possess high fungicidal activity [9]. It is reported that certain amino acid derivatives of 1,4-naphthoquinone are carriers of cerebroprotective, fungicidal, bactericidal, antitumor, antiinflammatory, antiischemic, antihypoxic, anticonvulsant activity and exhibit a stimulating effect on the blood supply to the brain [10]. Also, N-1,4-naphthoquinone derivatives are characterized by moderate toxicity [11].

All these facts raise interest in the synthesis of some amino acid derivatives of 1,4-naphthoquinon and further study their biological activity.

EXPERIMENTAL SECTION

Thermographic studies were determined on derivatograph Q-1500D system "F. Paulik-Paulik-Erdey" with the registration of the analytical signal mass loss and thermal effects by using a computer. Samples of compounds were analyzed in dynamic mode with a heating rate of 10 ^{o}C/min in air. The mass of sample was 200 mg. The reference substance was aluminium oxide.

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.

Synthesis of 2-amino acid-3-chloro-1,4-naphthoquinones (4a-c)

To (0.022 mol) of 2,3-dichloro-1,4-naphthoquinone **1** dissolved in 50ml of DMSO added 10ml water solution (0.022 mol) of corresponding amino acids **5a-c**. The reaction was carried out by heating within 50 ^{o}C with stirring for 30 minutes. Then the reaction mixture mixed with 500 ml of water and 2g (0,015 mol) of K_2CO_3 were added. The precipitate was filtered. Filtrate - aqueous solution of salts of amino acid derivatives of 1,4-naphthoquinone were neutralized with 15% solution of HCl, precipitate filtered, washed with water and dried. Orange and red crystals were obtained with 51 - 55% yield.

3-[(3-dichloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl) amino]–acetic acid (4a)

Yield: 51 %; mp. 140 ^{o}C; Anal. Calcd. for $C_{12}H_8NO_4$: C, 54.26; H, 3.04; Cl, 13.35; N, 5.27. Found: C, 54.22; H, 3.09; Cl, 13.29; N, 5.31; IR (KBr): ν (cm^{-1}) 3344, 1720, 1672, 1592, 1564, 1420, 1248; 1108, 840; 720, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.09 (2H, d.d.,CH, Ar); 7,81 (2H, d.d., CH, Ar); 6.44 (1H, s., NH), 4,34 (2H, s., 2-CH).

3-[(3-dichloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl) amino]-propanoic acid (4b)

Yield: 55 %; mp. 153 ^{o}C; Anal. Calcd. for $C_{13}H_{10}NO_4$: C, 55.83; H, 3.60; Cl, 12.68; N, 5.01. Found: C, 55.78; H, 3.59; Cl, 12.69; N, 5.05; IR (KBr): ν (cm^{-1}) 3336, 1728, 1680, 1600, 1568, 1512, 1340; 1288, 1140; 724, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.08 (2H, d.d.,CH, Ar); 7,79 (2H, d.d., CH, Ar); 6.81 (1H, s., NH), 3,62 (2H, m., 3-CH), 2,33 (2H, t., 2-CH).

3-[(3-dichloro-1,4-dioxo-1,4-dihydronaphthalene-2-yl) amino]-butiric acid (4c)

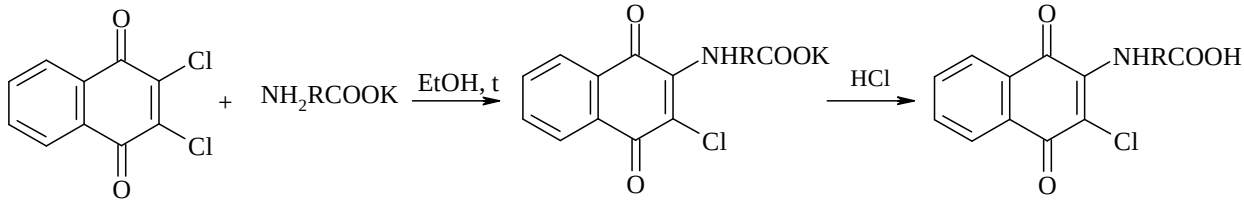
Yield: 54 %; mp. 164 ^{o}C; Anal. Calcd. for $C_{14}H_{12}NO_4$: C, 57.25; H, 4.12; Cl, 12.07; N, 4.77. Found: C, 57.28; H, 4.19; Cl, 12.09; N, 4.70; IR (KBr): ν (cm^{-1}) 3288, 1712, 1680, 1600, 1552, 1504, 1344, 1296, 1200, 728, 680; ^{1}HNMR ($(CD_3)_2SO$): δ ppm 8.10 (2H, d.d.,CH, Ar); 7,78 (2H, d.d., CH, Ar); 7,01 (1H, s., NH), 3,72 (2H, m., 4-CH), 2,36 (2H, t., 2-CH).2,19 (2H, m., 3-CH).

RESULTS AND DISCUSSION

Nucleophilic reagents such as aliphatic amino acids react with 2,3-dichloro-1,4-naphthoquinone **1**, replacing one chlorine atom. Electronic enrichment of quinones system affects the second chlorine atom reducing its activity towards nucleophiles [12].

It is known that the nucleophilicity of the amino group of free amino acids (zwitterionic form) is so low that the replacement of a chlorine atom in 2,3-dichloro-1,4-naphthoquinone **1** at amino acid residue not occurs. The conversion of amino acids into their salt provides increase of their nucleophilicity, enabling the nucleophilic substitution of chlorine atom of 2,3-dichloro-1,4-naphthoquinone **1** at amino acid fragment [13].

Synthesis of amino acid derivatives of 1,4-naphthoquinone **4a-c** were performed by the method **I** where initially aqueous solutions of amino acid salts **2a-c** were prepared, and then it was reacted with 2,3-dichloro-1,4-naphthoquinone **1** in alcohol with heating. Finally potassium salts of 2-amino acid-3-chloro-1,4-naphthoquinone **3a-c** were neutralized with 15% hydrochloric acid solution and free amino acid derivatives of 1,4-naphthoquinone **4a-c** were obtained. The resulting structure was purified by recrystallization from ethanol.



1 2 (a-c) 3 (a-c) 4 (a-c)

R = -CH_2- (à), -CH_2-CH_2- (b), -CH_2-CH_2-CH_2- (c).

Scheme 1 (method I)

To determine the purity of obtained by method **I** amino acid derivatives of 1,4-naphthoquinone **4a-c** physicochemical studies of thermographic parameters: weight loss and melting point were carried out.

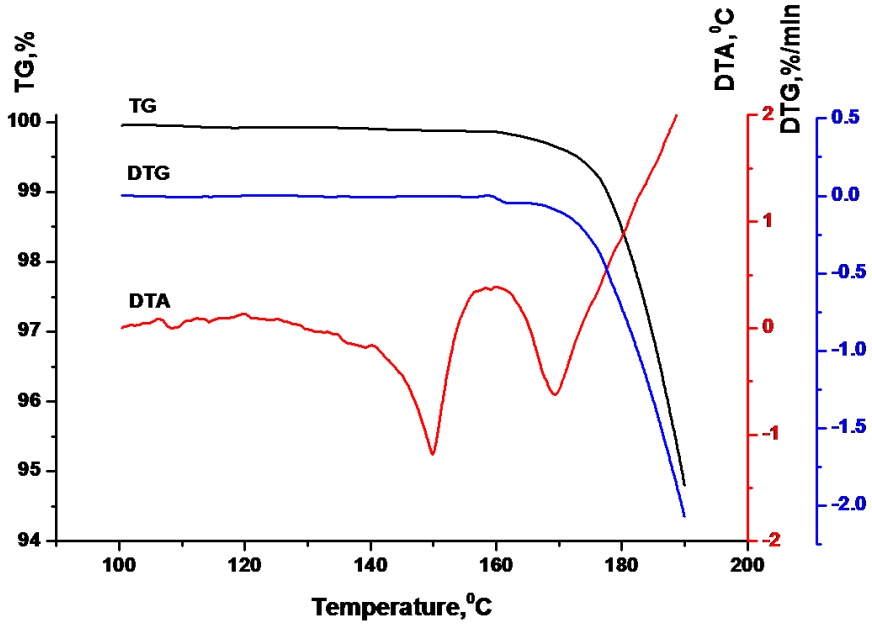
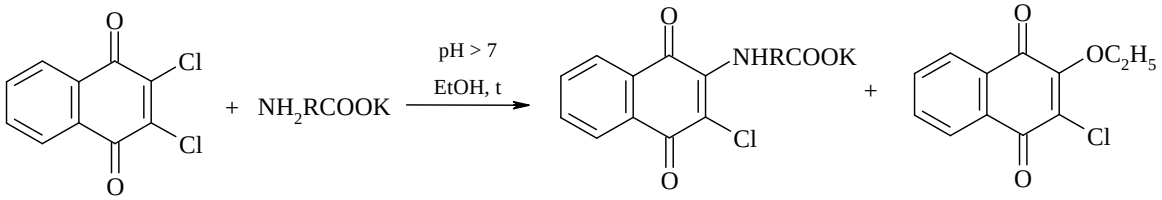


Figure 1. Thermogram of 3-[(3-chloro-1,4-dioxo-1,4-dihidronaphtalene-2-yl)amino]-propanoic acid (4b) obtained by the method I

Thermogravimetric curves (TG), which are present in tormogrames, show weight loss of samples during their heating, differential thermogravimetric curves (DTG) - correspond to the mass loss rate in depends on the temperature of the samples, and the curve of differential thermal analysis (DTA) corresponds to the temperature difference between the observed sample and standard (Al_2O_3) at the appropriate temperature.

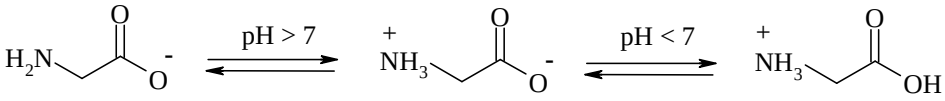
In thermographic curves (Fig. 1) observed two peaks, it indicates the presence of a impurity. Most likely in alkaline conditions can occur sided reaction to form 2-oxiethyl-3-chloro-1,4-naphthoquinone **5**, which has almost the same solubility as most amino acid derivatives of 1,4-naphthoquinone **4a-c** , which complicates the process of cleaning [14].



1 2 (a-c) 3 (a-c) 5

Scheme 2 (method I)

As it`s know amino acids in solution can have different forms depending on pH conditions (Scheme 3) [15].

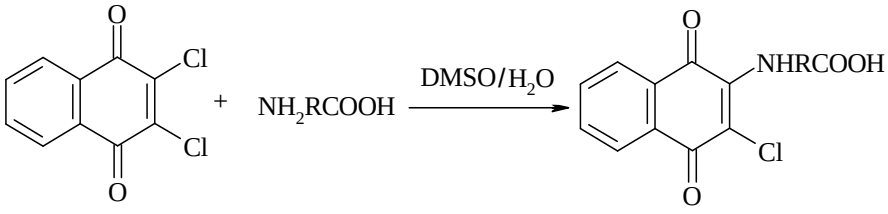


Anionic form Zwitterionic form Cationic form

Scheme 3

Therefore, synthesis of 2-amino acid-3-chloro-1,4-naphthoquinones **4a-c** by method **I** include alkaline conditions which are necessary for higher nucleophilicity of amino acids, but ethanol under alkaline conditions becomes reagent, not only solvent, and the result is a compound **5** (Scheme 2).

We have chosen synthesis conditions where side reactions could not occur. 2,3-Dichloro-1,4-naphthoquinone **1** were interacted with the appropriate free amino acids **6a-c** in dimethylsulfoxide/aqueous by heating (50 ^{0}C), which ensured the homogeneity of the reaction mixture, the reaction time was reduced to 30 minutes and 2-amino acid-3-chloro-1,4-naphthoquinone **4a-c** were obtained with good yields (above 50%).



1 6 (a-c) 4 (a-c)

R = -CH$_2$- (à), -CH$_2$-CH$_2$- (b), -CH$_2$-CH$_2$-CH$_2$- (c).

Scheme 3 (method II)

No catalytic systems in method **II** of synthesis amino acid derivatives of 1,4-naphthoquinone **4a-c** were used and obtained desired products did not require any purification. Accordingly, it demonstrates the high nucleophilicity and reactivity of free amino acids in the condition (pH 8-9) of dimethylsulfoxide.

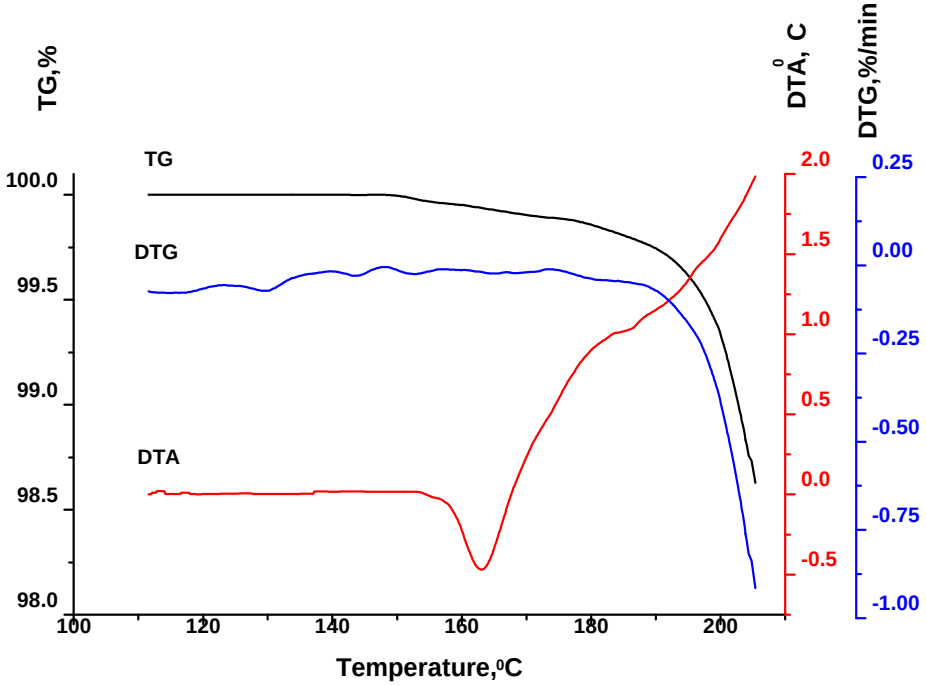


Figure 2. Thermogram of 3-[(3-chloro-1,4-dioxo-1,4-dihidronaphtalene-2-yl)amino]-propanoic acid (4b) obtained by the method II

Thermographic study of 2-amino acid-3-chloro-1,4-naphthoquinones **4a-c** obtained by the method **II**, confirmed their high purity and effectiveness of the proposed synthesis method.

Amino acids derivatives of 1,4-naphthoquinone **4a-c** have two active sites, which extends the possibilities for further modification with obtaining new potentially biologically active compounds.

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) belongs to naphthoquinone rings. The carboxyl group of compounds is depicted by single intensive peak at 1700-1740 cm^{-1}. The band at 3100 - 3400 cm^{-1} is due to valence vibration, and the band at 1520 cm^{-1} represents deformational vibrations of secondary NH groups. Presentes of C–Cl bond in 2-amino acid-3-chloro-1,4-naphthoquinone **4a-c** was proved absorption at 680 cm^{-1}. Absorption bands at 1400 and 726 cm^{-1} conforming the oscillations of -CH_2-groups in amino acid derivatives of 1,4-naphthoquinone [16].

In the ^{1}H NMR spectra two double duplets stretched within 8.1 - 7.7 ppm attributed to naphthoquinone fragments for all compounds **4a-c**. Protons of secondary amino groups were presented by broad singlet at 6.4 – 7.1 ppm. Signals of carboxyl groups in compounds **4a-c** were not seen, probably due to broadening of the peak resulting in proton exchange with solvent [17].

PREDICTION OF BIOLOGICAL ACTIVITY

The majority of biologically active compounds have both pharmacotherapeutic and side (toxic) actions. To estimate general efficacy and safety of the molecules under study, their biological potential should be thoroughly evaluated. Because the online based algorithm PASS [18] has been employed for preliminary evaluation of biological activity of synthesized amides based on amino acids derivatives of 1,4-naphthoquinone **4a-c**.

Table 1. Results predicted biological activity by screening program PASS (Pa> 0.7) of obtained compounds

Compound / PASS data	4a	4b	4c
Phobic disorders treatment	0,868	0,892	0,878
Gluconate 2-dehydrogenase (acceptor) inhibitor	0,840	0,826	0,839
CYP2J substrate	0,817	0,844	0,858
CYP2J2 substrate	0,820	0,851	0,866
DNA-(apurinic or apyrimidinic site) lyase inhibitor	0,860	0,819	0,767
Glycosylphosphatidylinositol phospholipase D inhibitor	0,842	0,771	0,743
Antiseborrheic	0,769	0,722	
Phthalate 4,5-dioxygenase inhibitor	0,837	0,723	
Chlordecone reductase inhibitor	0,741	0,705	
2-Hydroxyquinoline 8-monooxygenase inhibitor	0,774		
Fructose 5-dehydrogenase inhibitor	0,768		
Creatininase inhibitor	0,756		
Proteasome ATPase inhibitor	0,801		
Carboxypeptidase Taq inhibitor	0,727		
Pseudolysin inhibitor	0,723		
Arylsulfate sulfotransferase inhibitor	0,825		
Membrane permeability inhibitor			0,733
Mucomembranous protector		0,746	0,768

According to calculations performed by PASS program it was discovered that some compounds are good candidates for different biological activities mostly associated with antibacterial and antifungal because of predicted inhibitory effect on gluconate 2-dehydrogenase, which suppresses growth of microorganisms [19, 20]. Also, compounds may exhibit some activity in prevention of phobic disorders, mucomembranous protection, inhibition of transcription factor, wide range of enzymatic activity and others (Table 1).

CONCLUSION

Synthesis of a series of 2-amino acid-3-chloro-1,4-naphthoquinones demonstrated possibility to perform reactions in mild conditions with relatively high yields, simple procedure and low time costs. Results of predicted biological activity of amino acid derivatives of 1,4-naphthoquinone are going to be used as a basis for determination further experimental biological research. 2-Amino acid-3-chloro-1,4-naphthoquinones could be used for synthesis and development of highly efficient new biologically active agents.

REFERENCES

[1] V Tandon; H Maurya; M Verma; R Kumar; P Shukla. *E. J Med. Chem*., **2010**, 45 (6), 2418-2426.
[2] MV Stasevych; VG Chervetsova; MYu Plotnikov; MO Platonov; SI Sabat; RYa Musyanovych; VP Novikov. *Ukr. Bioorg. Acta*, **2006**, 4(2), 33-39.
[3] A Mantyla; T Garnier; J Rautio; T Nevalainen; J Vepsalainen; A Koskinen; SI Croft; T Jarvinen. *J. Med. Chem*., **2004**, 47(1), 188-195.

[4] V Prachayasittikul; R Pingaew; A Worachartcheewan; C Nantasenamat; S Prachayasittikul; S Ruchirawat; V Prachayasittikul. *E. J. Med. Chem.*, **2014**, 84, 247-263.
[5] P Ravichandiran; J Athinarayanan; D Premnath; V Periasamy; A Alshatwi; S Vasanthkumar. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, **2015**, 139, 477–487.
[6] V Tandon; D Yadav; H Maurya; A Chaturvedi; P Shukla. *Bioorg. Med. Chem.*, **2006**, 14(17) 6120–6126.
[7] T Sreelatha; S Kandhasamy; R Dinesh; S Shruthy; S Shweta; D Mukesh; D Karunagaran; R Balaji; N Mathivanan; PTh Perumal. *Bioorg. Med. Chem. Lett*., **2014**, 24(15), 3647–3651.
[8] TMS Silva; CA Camara; TP Barbosa; AZ Soares; LC Cunha; AC Pinto; MD Vargas. *Bioorg. Med. Chem*., **2005**, 13(1), 193-196.
[9] N Sundholm; A Smith. *J. Chem. Soc*., **1951**, 73, 3459-3462.
[10] AP Kartoflitskaya; VT Kolesnikov; VN Solonin; LA Kucherenko; AA Guzova; VM Shelevyi; MK Khmeliuk; VL Belyaev. *A.s. 1774617 (USSR)*, **1983**.
[11] AP Kartoflytskaya; GI Stepanyuk; VV Yushkova NG Marintsova; VP Novikov. *Chem. Pharm. J*., **1997**, 31, 6-17.
[12] T Win; S Bittner. Tetrahedron lett., **2005**, 46, 3229-3231.
[13] C Ibis; AF Tuyun; H Bahar; SS Ayla, MV Stasevych; RYa Musyanovych; O Komarovska-Porokhnyavets; V Novikov. *Med. Chem. Res*., **2013**, 22(6), 2879–2888
[14] ZV Gubriy; VZ Klep; BL Litvin; VP Novikov. *Russian J. Org. Chem.*, **1996**, 32(6), 916.
[15] W Simmons; G Meisenberg. Principles of medical biochemistry, Mosby Elsevier, 2006; 19.
[16] T Pliev. *Appl. Spectroscopy*, **1970**, 13, 124-129.
[17] Y Volovenko; O Turov. Nuclear magnetic resonance, (in Ukrainian), Perun, Kiev, **2007**.
[18] A Sadym; A Lagunin; D Filimonov; V Poroikov. *Pharm. Chem. J*., **2002**, 36(10), 21-26.
[19] CA Westby; DS Cutshall; GV Vigil. *J. Bacteriol*, **1983**, 156(3), 1369-1372.
[20] DL Purich; RD Allison. The enzyme reference: a comprehensive guidebook to enzyme nomenclature, reactions, and methods. Academic Press, **2002**; 364.