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Synthesis and properties of 3-amino-2-(3,5-di-*tert*-buthyl-4-hydroxyphenil)-1,4-naphthoquinones

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Novel biologically active 3-amino-2-(3,5-di-*tert*-buthyl-4-hydroxyphenil)-1,4-naphthoquinones were obtained by reaction of 3-chloro-2-(3,5-di-*tert*-buthyl-4-hydroxyphenil)-1,4-naphthoquinone with various amines and amino acids. Compounds were characterized with standard methods of chemical analysis and spectroscopic techniques. Synthesis of a series 3-amino- and 3-amino acid-2-(3,5-di-*tert*-buthyl-4-hydroxyphenil)-1,4-naphthoquinones demonstrated feasibility to conduct reactions in mild conditions providing relatively high yields in simple procedure and low time costs. Both fungicidal and antibacterial activity of these novel compounds 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. It was found that substances 4**a, 4b, 4d, 5a, 5b** had moderate antibacterial activity against Gram-positive bacteria *S. aureus, M. luteum.* Compound **5d** showed strong effect on *M. luteum* with the minimum bacteriostatic concentration of 62.5 mg/ml. The culture of Gram-negative bacteria *E. coli* proved resistance against compounds 5**a-d,** however compounds **4a-d** demonstrated moderate bactericidal activity against *E. coli*. The synthesized compounds 4**a-d** and **5a-d** showed fungicidal effect on the growth of yeasts *C. tenuis,* but did not prevent growth of *A. niger.* Some of tested compounds showed significant inhibitory effect on receptor tyrosine kinase (RTK). In particular, compounds **5a** and **5e** inhibited tyrosine kinase activity by 57 and 51%, respectively. More powerful inhibitory effect of 75% was observed for compound **4a**. Found that compounds **5b** and **5c** inhibit oxidative processes in tissues and some indicators of antioxidant action exceeded quercetin results.

Keywords: 1,4-naphthoquinones, hindered phenols, amines, amino acids.

INTRODUCTION

1,4-Naphthoquinone or para-naphthoquinone is known as an important core structure of many natural compounds, including the most notable member representing vitamin K [1]. The other well-known natural naphthoquinones comprised by chemical structures of juglone, plumbagin, and droserone. Various naphthoquinone derivatives possess significant pharmacological activities exerting cytotoxic, antibacterial, antifungal, antiviral, insecticidal, anti-inflammatory, and antipyretic properties. Plants containing naphthoquinone are widely used as folk medicine in China and South America for treatment of malignant and parasitic diseases [2].

Natural 1,4-naphthoquinones often possess beneficial combination of various useful properties due to electrophilic C=C bounding. For example, 3-hydroxy-2-(3,5-di-*tert*-buthyl-4-hydroxyphenil)-1,4-naphthoquinone combines properties of cancer cell growth inhibitor [3] and strong antioxidant [4]. Presence of sterically hindered phenol in this derivative of naphthoquinone is most likely responsible for the antioxidant activity. The role of phenolic structures in this regard could be of particular interest since the discovery of its presence in α-tocopherol (vitamin E) representing one of the major free radical chain-breaking antioxidant in human blood. Therefore incorporation of strerically hindered phenols into 1,4-naphthoquinones appear to be very meaningful in terms of broadening their biological activity. However, the excessive toxicity of some 1,4-naphthoquinones has limited their application. Therefore, search for more potent and less toxic 1,4-naphthoquinones is very important. One of the possible ways to achieve this goal is to synthesize novel amino-substituted derivative of 1,4-naphthoquinone. N-derivatives of 1,4-naphthoquinone could be used as possible approach to diverse biological activity and attenuate toxicity [5].

The present study is devoted to synthesis and characterization of biological properties novel N-derivatives of 1,4-naphthoquinone containing 2,6-di-*tert*-buthylphenol moiety. Our goal here was to study the effect of presence both sterically hindered phenol and primary or secondary amines on pharmacological activity of 1,4-naphthoquinone.

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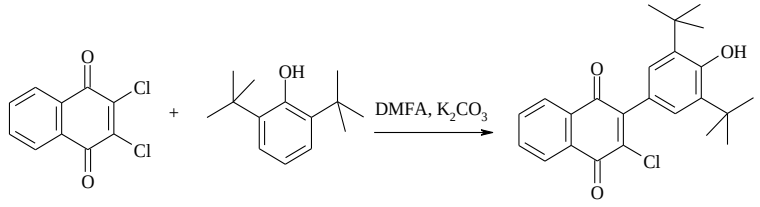


1 2 3

Scheme 1

2. RESULTS AND DISCUSSION

2.1. Synthesis

Starting 3-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphthoquinone (**3**) was obtained (Scheme 1) by reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) with 2,6-di-*tert*-butylphenole (**2**) as described earlier [6] with minor modification. The further reaction of compound (**3**) with corresponding primary and secondary amines allowed obtaining several different products (**4a-e**). The reaction (Scheme 2) was carried out in boiling toluene at presence of triethylamine employed as HCl acceptor.

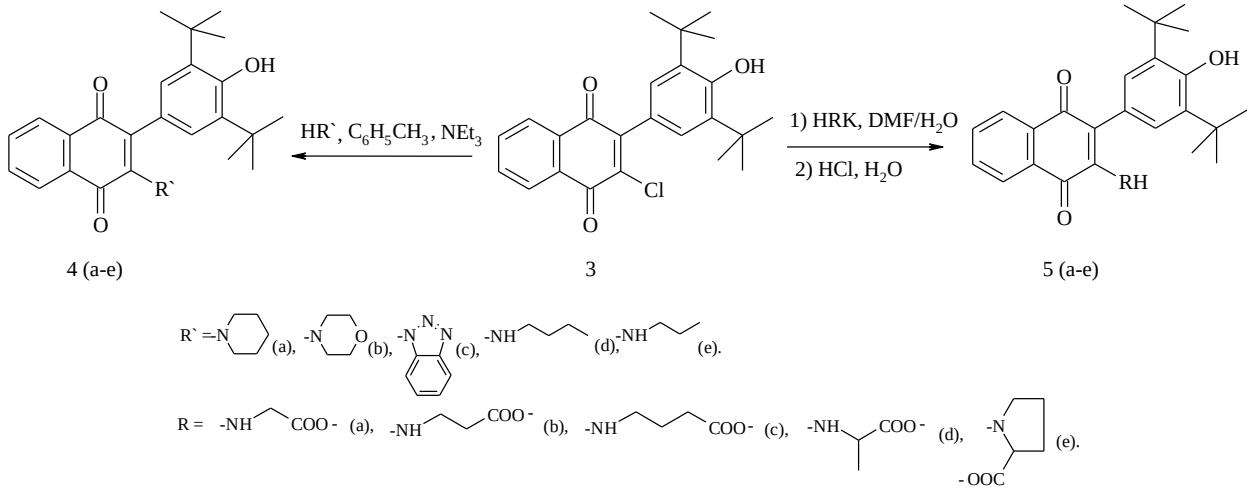
To obtain other N-derivatives of 1,4-naphthoquinone (**5a-e**) by reaction of 3-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphthoquinone (**3**) with corresponding salts of amino acids ethanol [7-8] was replaced by dimethylformamide/water system (Scheme 2), to eliminate possible side reaction with formation an additional product - 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-ethoxy-1,4-naphthoquinone [4]. The synthesis was performed in neutral conditions by using salts of amino acids, because the substitution of chlorine atom in 3-chloro-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphthoquinone (**3**) with amino group requires much higher nucleophilicity than that presented by its zwitterionic form, the reactivity of amino acid was reinforced by neutralization with potassium hydroxide making participation of amino acids in reaction as a base instead of acid [9].

Potassium salts of 3-amino acid-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphthoquinones were neutralizing with hydrochloric acid and desired 3-amino acid-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphthoquinones (**5a-e**) were obtained with sufficient yields (35 – 46%).

2.2. Spectral data (analysis)

The IR spectra of all synthesized molecules showed intense absorption peaks representing hindered hydroxyl group (3624-3600 cm^{-1}) and stretching vibrations of CH-bonds of 1,4-naphthoquinone (3050 cm^{-1}) as well as valence CH-vibrations of methyl groups (2900-2850 cm^{-1}). The absorption band of medium intensity at 1350-1320 cm^{-1} represents CH deformation vibrations of the methyl groups. In the range of 1265-1210 cm^{-1} there were two absorption bands of medium intensity associated with Ar-OH fluctuations of steric-hindered phenols. Presence of another two groups of bands at 885-870 and 830-815 cm^{-1} can be explained by non-planar deformational vibrations of substituted benzene ring [10]. Two pairs of peaks at 1680 and 1640 cm^{-1} (C=O) and 1600 and 1560cm^{-1} (C=C) belong to naphthoquinone and phenolic rings.

The carboxyl group of compounds **5a-e** is depicted by single intensive peak at 1700-1740 cm^{-1}. The band at 3352 cm^{-1} is due to valence vibration,



4 (a-e) 3 5 (a-e)

Scheme 2

and the band at 1520 cm^{-1} represents deformational vibrations of secondary NH groups not applicable for amino acid derivatives that containe proline and others (**4a-c**, **5e).**

The absence of C–Cl bond in 3-N-derivatives-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphthoquinone (**4a-e, 5a-e**) was proved by lack of absorption at 680 cm^{-1}. Instead of it, there were absorption bands at 1400 and 726 cm^{-1} conforming the oscillations of -CH_2-groups in compounds **4a**, **4b**, **4d**, **4e**, **5a**, **5b**, **5c**, **5d** [11].

The ^{1}H NMR spectra revealed proton signals of methyl *tert*-butyl groups depicted by singlet at 1.4-1.5 ppm. Protons of OH group are characterized by singlet at 5.2 – 6.4 ppm belonging to sterically hindered phenols. Protons of naphthoquinone fragments for all compounds showed by two double duplets stretched within 8.6 - 7.6 ppm. Protons of secondary amino groups in compounds **4d-e**, **5a-d** were presented by signals at 5.9 and 6.7 ppm, respectively. Signals of carboxyl group in compounds **5a-e** were depicted by singlet at 12-13 ppm [12].

2.3. Prediction of biological activity

Online-based algorithm PASS [13] has been employed for preliminary evaluation of biological activity of synthesized molecules. It was discovered that all compounds are good candidates for different biological activities mostly associated with antioxidant properties as it was expected from the beginning. Some other biological properties were predicted including most potent antibacterial and fungicidal activity and inhibitory effect on cell signaling involved receptor tyrosine kinases. Also, compounds may exhibit some activity in prevention of myocardial ischemia, inhibition of transcription factor, inhibition of lipid peroxidase and mucomembranous protection.

2.4. Testing of biological activity

Both fungicidal and antibacterial activity of novel compounds (**4a-e**), (**5a-e**) and starting substance **3** 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 substances **4b, 4d, 4e, 5a, 5b** had moderate antibacterial activity against gram-positive bacteria *S. aureus, M. luteum.* Compound **5d** showed a strong effect on *M. luteum* with the minimum bacteriostatic concentration of 62.5 mg/ml. The culture of gram-negative bacteria *E. coli* proved resistance against compounds (**5a-e),** however compounds (**4a-e)** demonstrated moderate bactericidal activity against *E.coli*.

Some of the synthesized compounds (**4a-e)** and (**5a-e)** showed fungicidal effect on the growth of yeasts *C. tenuis* but did not hinder the growth of *A. niger.*

2.5. Evaluation of enzymatic activity

The possible effect of novel compounds on cell signaling involved receptor tyrosine kinases was studied as described in [15]. Some of tested compounds showed significant inhibitory effect on receptor tyrosine kinase (RTK). In particular, compounds **5a** and **5e** inhibited tyrosine kinase activity of proteins in membrane fractions by 57 and 51%, respectively (Table 1). More powerful inhibitory effect, reducing the basal level of 75% was noticed for compound **4a**. Such inhibitory effect is subject for further research of these compounds as promising pharmacological agents for effective correction of pathological conditions associated with excessive activity of the RTK.

2.6. Evaluation of antioxidant activity

The purpose of this study was to investigate the antioxidant activity (AOA) of newly obtained naphthoquinone derivatives (**4a-e**)**,** (**5a-e)** and synthesized earlier compound **3** terms of initiating free radical oxidation *in vitro*. To assess the direction of these changes, we used two indicators of oxidative stress: content of peroxide groups in lipids and products of their metabolism - thiobarbiturate-active products (TBA) and the content of carbonyl groups (CG) in proteins.

The study was carried out on chicken liver homogenates. Determination of both indicators of oxidative stress was performed in one test [16]. Amount of protein in the sample was determined by the method of Lowry. Statistical analysis of the results was performed using Student t-test.

Among a number of the compounds revealed that compounds **5b** and **5c** show antioxidant properties of two parameters, as observed a significant reduction of TB-active products and formation CG compared with controls, indicating a decrease in the intensity of LPO and OMP. Also established that compound **5e** causes intensification of
LPO and OMB, which increases the content free radical oxidation of lipids and proteins products by 50% (Table 1).

In our opinion compounds **5a**, **5b**, **5c**, **7e**, **8** show potent oxidation activity due to the lack of a hydrogen atom at the amino group. This makes it

impossible to shift the position of hydrogen in the 4-position with the formation of hydroxyl group.

3. CONCLUSION

Synthesis of a series 3-amino- and 3-amino acid-2-(3,5-di-*tert*-buthyl-4-hydroxyphenyl)-1,4-naphthoquinones demonstrated possibility to perform reactions in mild conditions with relatively high yields, simple procedure and low time cost. Results on antibacterial, antifungal, enzymatic and antioxidant activity tests showed capacity of novel compound to be used as a basis for further development of highly efficient biologically active agents.

4. MATERIAL AND METHODS

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-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-NR-[1,4]-naphtho-quinones (4a-e)

The 5 mol solution of 2-chloro-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-1,4-naphtoquinone prepared in 10 ml of toluene was mixed with 6 mol of corresponding amine and with 6.5 mol of triethylamine. The reaction mixture was boiled for 2 hours, cooled, and filtered. The solvent was evaporated under vacuum, and the residue was recrystallized from acetone.

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-piperidinyl-1-[1,4]-naphthoquinone (4a)

Yield: 84 %; mp. 167-169 ^{0}C; Anal. Calcd. for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 10.77. Found: C, 78.32; H, 7.99; N, 10.61; IR (KBr): ν (cm^{-1}) 3608, 3040-2800, 1688, 1672, 1600, 1572, 1408, 1340, 1124, 904, 728; ^{1}HNMR ($CDCl_3$): δ ppm 1,41 (18H, s., CH, t-Bu); 1,54 (6H, m., CH); 2,88 (4H, br.s.,CH_2); 5,28 (1H, s., OH); 7,06 (2H, s., Ph); 7,65 (2H, m., Ar); 8,06 (2H, m., Ar).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-morpholinyl-1-[1,4]-naphtho-quinone (4b)

Yield: 88 %; mp. 170-172 ^{0}C; Anal. Calcd. for $C_{28}H_{33}NO_4$: C, 75.14; H, 7.43; N, 14.30. Found: C, 75.31; H, 7.49; N, 14.06; IR (KBr): ν (cm^{-1}) 3600, 3040-2800, 1680, 1676, 1596, 1404, 1320, 1116, 896, 732; ^{1}HNMR ($CDCl_3$): δ ppm 1,47 (18H, s., CH, t-Bu); 2,97(4H, t., CH); 3,97(4H, t., CH); 5,32 (1H, s., OH); 7,07 (2H, s., Ph); 7,67 (2H, m., Ar); 8,59 (2H, m., Ar).

2-Benzothriazolyl-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-[1,4]-naphtho-quinone (4c)

Yield: 74 %; mp. 183-185 ^{0}C; Anal. Calcd. for $C_{30}H_{29}NO_3$: C, 75.13; H, 6.10; N, 8.76. Found: C, 75.30; H, 6.25; N, 8.65; IR (KBr): ν (cm^{-1}) 3604, 3040-2800, 1678, 1608, 1400, 1320, 1246, 894; ^{1}HNMR ($CDCl_3$): δ ppm 1,38 (18H, s., CH, t-Bu); 4,72 (1H, s., OH); 7,19 (2H, s., Ph); 7,61 (2H, m., Ar); 7,84 (2H, m., Ar); 8,23 (2H, m., Ar); 8,32 (2H, m., Ar).

Table 1. Results of experimental biological research of obtained compounds.

№	Biological activity						Enzymatic activity (%)	Antioxidant activity	
	Fungicidal	Antibacterial							
	C. tenuis	*S. aureus*		*E. coli*	*M. luteum*			TBA (%)	CG (%)
	Concentration of compound (%)								
	0.5	0.5	0.1	0.5	0.5	0.1			
Control	-	-	-	-	-	-	100 ± 16	100±7.3	100±7.8
3	20	16	8	13	12	0	106 ± 17	126±13.9	31±14.8
4a	0	13.4	7	10	13.7	8	**28 ± 9**	123±12	131±8.4
4b	0	14.8	10	10.7	15	7	58 ± 11	130±7.5	133±10.5
4c	17.2	9.8	0	8	9	0	91 ± 18	128±3.5	141±8.4
4d	14	10.5	0	7	16	8	83 ± 19	89.7±6	107±6.7
4e	18	16.5	0	9.5	20	12	86 ± 15	96±10.3	112±5.9
5a	0	15.7	0	0	8.7	0	**42 ± 8**	100±4.4	92 ±8.6
5b	0	15.0	0	0	11.4	0	60 ± 15	**93.6±6.5**	**89±8.8**
5c	0	0	0	0	10.7	0	63 ± 17	**87±5.5**	**91±6.4**
5d	13	0	0	0	**27.0**	19.0	67 ± 8.5	77±6.4	103±12.8
5e	0	0	0	0	0	0	**45 ± 10**	147±13.1	154±9.25
Quercetine	-	-	-	-	-	-	-	103±6.4	59±13.2

2-Butylaminoyl-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-[1,4]-naphthoquinone (4d)

Yield: 81 %; mp. 130-132 ^{0}C; Anal. Calcd. for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14; N, 3,23. Found: C, 77.72; H, 8.25; N, 3,09; IR (KBr): ν (cm^{-1}) 3612, 3000-2800, 1684, 1668, 1612, 1404, 1324, 904, 728; ^{1}HNMR ($CDCl_3$): δ ppm 0,69 (т., *J* = 7,3, CH, n-Bu, 3H); 1,01(m., CH, n-Bu, 2H); 1,22 (t., CH, n-Bu, 2H); 1,41 (18H, c., CH, t-Bu); 2,56 (2H, m., CH, n-Bu); 6,48 (1H, s., OH); 6,71 (1H, s., NH); 6,91 (2H, s., Ph); 7,65 (1H, t, *J* = 7,5 Hz, Ar); 7,74 (1H, t., *J* = 7,5 Hz, Ar); 7,97 (2H, dd., *J* = 16,8; 7,6 Hz, Ar).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-3-ethylamino-[1,4]-naphthoquinone (4e)

Yield: 85 %; mp. 127- 129 ^{0}C; Anal. Calcd. for $C_{26}H_{31}NO_3$: C, 77.02; H, 3.45; N, 7.71. Found: C, 77.20; H, 3.31; N, 7.84; IR (KBr): ν (cm^{-1}) 3605, 3000-2800, 1680, 1662, 1608, 1412, 1328, 900, 724; ^{1}HNMR ($CDCl_3$): δ ppm 1,22 (3H, t., *J* = 7,6 Hz, CH_3); 1,39 (18H, s., CH, t-Bu); 3,56 (2H, m., CH_2); 6,38 (1H, s., OH); 6,81 (1H, s., NH); 6,99 (2H, s., Ph); 7,68 (1H, t., *J* = 7,4 Hz, Ar); 7,76 (1H, t., *J* = 7,3 Hz, Ar); 8,05 (2H, dd., *J* = 7,4 Hz, Ar).

Synthesis and purification of 3-amino acid sabstituted-2-(3,5-di-*tert*-buthyl-4-hydroxyphenyl)-[1,4]-naphthoquinones (5a-e)

Equimolar amounts (0.012 mol) of compound (**3**) and corresponding salts of aliphatic amino acids were heated at 70^{0}C in system DMF/water (5:1) for 3 hours. Reaction mixture was mixed with water (500 ml) and filtered. Filtrate was purified by extraction with dichloromethane (1:1). The salts of amino acid derivatives were neutralized and precipitated from water phase with HCl and dried.

[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,4-dioxo-1,4-dihydronaphtalenyl-2-amino]-acetic acid (5a)

Yield: 40 %; mp. 187-189 ^{0}C; Anal. Calcd. for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.58; H, 6.63; N, 3.29; IR (KBr): ν (cm^{-1}) 3632, 3338, 3056, 1722, 1672, 1576, 1504, 1345, 1292, 1236, 728; ^{1}HNMR (DMSO-d_6): δ ppm 12,89 (1H, s., COOH); 8,00 – 7,94 (2H, m., CH, Ar); 7,88 – 7,79 (2H, m., CH, Ar); 7,28 (1H, s., NH); 7,05(1H, s., OH); 6,89 (2H, s., CH, Ar); 4,40 – 4,36 (2H, d., α-CH_2); 1,35 (18H, s., t-Bu).

[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,4-dioxo-1,4-dihydronaphtalenyl-2-amino]-propionic acid (5b)

Yield: 43 %; mp. 157-159 ^{0}C; Anal. Calcd. for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95 N, 3.12. Found: C, 72.05; H, 7.05; N, 3.04; IR (KBr): ν (cm^{-1}) 3560, 3352, 2936, 1720, 1680, 1632, 1592, 1568, 1504, 1432, 1344, 1296, 1232, 728; ^{1}HNMR (DMSO-d_6): δ ppm 12,43 (1H, s., COOH); 8,03 – 7,95 (2H, m., CH, Ar); 7,86 – 7,73 (2H, m., CH, Ar); 7,28 (1H, s., NH); 7,09 (1H, s., OH); 6,95 (2H, s., CH, Ar); 3,95 – 3,81 (2H, q., β-CH_2); 2,61 – 2,54 (2H, t., α-CH_2); 1,36 (18H, s., t-Bu).

[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,4-dioxo-1,4-dihydronaphtalenyl-2-amino]-bytyric acid (5c)

Yield: 46 %; mp. 191-193 ^{0}C; Anal. Calcd. for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.18 N, 3.02. Found: C, 72.58; H, 7.06; N, 3.05; IR (KBr): ν (cm^{-1}) 3632, 3328, 2956, 1704, 1672, 1568, 1520, 1248, 1292, 728; ^{1}HNMR (DMSO-d_6): δ ppm 12,01 (1H, s., COOH); 8,01 – 7,93 (2H, m., CH, Ar); 7,85 – 7,73 (2H, m., CH, Ar); 7,12 (1H, s., NH); 7,02(1H, s., OH); 6,94 (2H, s., CH, Ar); 3,75 – 3,61 (2H, q., ɤ-CH_2); 2,61 – 2,59 (2H, t., α-CH_2); 1,75 - 1,70 (2H, m., β-CH_2); 1,38 (18H, s., t-Bu).

2-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,4-dioxo-1,4-dihydronaphtalenyl-2-amino]-propionic acid (5b)

Yield: 38 %; mp. 134-136 ^{0}C; Anal. Calcd. for $C_{27}H_{31}NO_5$: C, 71.14; H, 6.95 N, 3.12. Found: C, 71.19; H, 6.95; N, 3.07; IR (KBr): ν (cm^-1) 3632, 2952, 2760, 1728, 1680, 1632, 1600, 1568, 1520, 1456, 1336, 1232, 728; ^{1}HNMR (DMSO-d_6): δ ppm 12,88 (1H, s., COOH); 8,05 – 7,99 (2H, m., CH, Ar); 7,87 – 7,76 (2H, m., CH, Ar); 7,22 (1H, s., NH); 7,10 (1H, s., OH); 7,05 (2H, s., CH, Ar); 4,59 – 4,43 (1H, m., α-CH); 1,55 – 1,51 (3H, d., CH_3); 1,40 (18H, s., t-Bu).

1-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-1,4-dioxo-1,4-dihydronaphtalenyl-2]-pyrrolidine-2-carboxyc acid (5e)

Yield: 35 %; mp. 133-136 ^{0}C; Anal. Calcd. for $C_{29}H_{33}NO_5$: C, 73.24; H, 6.99 N, 2.95. Found: C, 72.98; H, 7.08; N, 3.07; IR (KBr): ν (cm^-1) 3632, 2944, 2912, 2416, 1744, 1696, 1332, 1304, 1272, 816, 724; ^{1}HNMR (DMSO-d6): δ ppm 12,98 (1H, s., COOH); 7,99 – 7,93 (2H, m., CH, Ar); 7.78 – 7,67 (2H, m., CH, Ar); 7,14 (2H, s., CH, Ar); 5,75 (1H, s., OH); 3,85 – 3,80 (2H, t., δ-CH_2); 4,35 – 4,29 (1H, t., α-CH); 2,38 – 2,29 (2H, q., β-CH_2); 2,00 – 1,90 (2H, m., ɤ-CH_2); 1,42 (18H, s., t-Bu).

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СИНТЕЗА И СВОЙСТВА НА 3-АМИНО-2-(3,5-ДИ-*tert*-БУТИЛ-4-ХИДРОКСИФЕНИЛ)-1,4-НАФТОХИНОНИ

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(Резюме)

Получени са нови биологично-активни вещества - 3-амино-2-(3,5-ди-*tert*-бутил-4-хидроксифенил)-1,4-нафтохинони чрез реакция на 3-хлоро-2-(3,5-ди-*tert*-бутил-4-хидроксифенил)-1,4-нафтохинони с различни амини и аминокиселини. Съединенията са охарактеризирани със стандартни методи на химични анализи и спектроскопия. Синтезата на серия от 3-амино- and 3-аминокиселинни -2-(3,5-ди-*tert*-бутил-4-хидроксифенил)-1,4-нафтохинони показва възможността да се водят реакциите при меки условия с високи добиви, с проста процедура и кратко време. Изпитани са фунгицидната и антибактериалната активност на тези нови съединения върху култури, развити в агар: *Escherichia coli, Staphylococcus aureus, Mycobacterium luteum* и гъбичките *Candida tenuis, Aspergillus niger* по стандартни методики. Намерено е, че веществата **5a, 5b, 5d, 7a, 7b** имат умерена антибактериална активност срещу Грам-положителните бактерии *S. Aureus* и *M. luteum.* Съединение **7d** показва най-силен ефект спрямо *M. luteum* с минимум бактериостатична концентрация 62.5 mg/ml. От Грам-отрицателните бактерии *E. coli* показва резистентност спрямо съединения **7a-d,** но съединенията **5a-d** показват умерен бактерицидна активност спрямо *E. coli*. Синтезираните съединения **5a-d** и **7a-d** показват фунгициден ефект към растежа на дрождите *C. tenuis,* но не предотвратява растежа на *A. niger*. Някоио от изпитаните съединения показват значителен инхибиращ ефект върху рецепторната тирозин-киназа (RTK). В частност съединенията **7a** и **7e** инхибират тирозин-киназната активност със съответно 57 и 51%. Най-мощен инхибиращ ефект от 75% са наблюдавани за съединение **5a**. Намерено е, че съединенията **7b** и **7c** инхибират окислителните процеси в тъканите и някои индикатори на антиоксидантната активност превишават резултатите за куерцетина.