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Syntesis and antimicrobial evaluation of novel 2-substituted-3-mercapto-1,4-naphthoquinones

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Summary. A series of 2-substituted-3-mercapto-1,4-naphthoquinones were synthesized and evaluated for their antimicrobial activities. The detailed synthetic protocol, spectroscopic and antimicrobial data are reported. 2-Morpholino-3-mercapto-1,4-naphthoquinone and 2-piperydyno-3-mercapto-1,4-naphthoquinone showed greater antibacterial activity than well known antibiotic oxacillin. The quantum-chemistry calculations were carried out using semi-empirical PM3 method to study the molecular geometry and electronic structure of obtained thiols. Biological activity prediction using computer program *PASS C&T* was performed, made and indicated the necessity of further investigation of new synthesized compounds.

Keywords: thiol, naphthoquinone, antimicrobial activity, *PASS C&T*.

Introduction. Sulfur containing compounds and naphthoquinones have been the subject of much interest for a number of years due to their antimicrobial, antiviral, anti-inflammatory biological activities [1-4]. 1,4-Naphthoquinone pharmacophore is known to impart cytotoxity in a number of drugs, for example, streptonigrin [5], actinomycins [6], mitomycins [7], alkannins [8], 2-hydroxynaphthoquinones derivatives [9] and 1,4-furanonaphthoquinones [10]. In addition to imparting antifungal and cytotoxic activity 1,4-naphtoquinones have also exhibited significant antimicrobial activity [11].

Due to high lability of S-H and C-S bonds, their ability to be scission under action of the nucleophilic and electrophilic reagents makes thiols valuable for synthesis and evaluation. The combination of S-H bond and naphthoquinone fragment will allow different chemical transformations and would expand the spectrum of biological action. Only 2-amino-3-mercapto-1,4-naphthoquinone (**2a**) and 2-anilino-3-mercapto-1,4-naphthoquinone (**2f**) are described in the literature [12, 13].

Therefore, why our work reports the synthesis and antibacterial evaluations for previously synthesized and new 2-substituted-3-mercapto-1,4-naphthoquinones.

Results and discussion. 2-Amino- **3a-g** and 2-hydroxy-3-mercapto-1,4-naphthoquinones **3k** (Scheme 1) were obtained previously by us [14] similar to methods [15, 16] by the interaction of **2a-g,k**: A — with sodium sulfide in water, followed by acidification of the reaction mixture; B — with thiourea in alcohol, alkaline hydrolysis of isothiuronic salts and acidification of the reaction mixture.

2a, f obtained by the method A were described in literature [12, 13] earlier.

2,3-Dichloro-1,4-naphthoquinone **1** (DCNQ) was used as an initial compound for synthesis of thiols. The preparation of **2a-g** from **1** was modernized and the yields and purity of products improved [17].

Compounds **3a-o** also were obtained from

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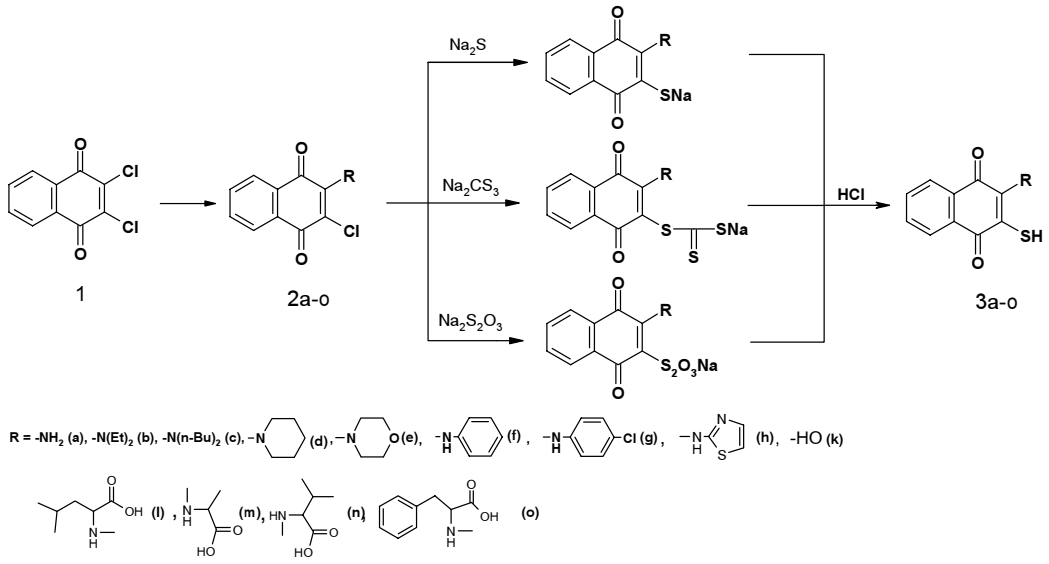
Scheme 1

Synthesis of 2-substituted-3-mercapto-1,4-naphthoquinones



2a-o using sodium trythiocarbonate [18] and Bunte salts [19, 20] following by acidication of reaction mixture.

Thiol derivatives of aminoacid substituted-1,4-naphthoquinone **3l-o** were synthesized for the first time. Comparison of methods of thiols synthesis has shown that the use of sodium sulfide in DMF as a solvent is optimal.

Molecular modeling analysis. The quantum-chemistry calculations were carried out to study the molecular geometry and electronic structure of thiols **3d,e,h-l,n** using *HyperChem* 7 [21]. Full geometry optimization was performed using semi-empirical PM3 method (RMS gradient of 0.001 kcal/Å mol). The total energy, electronic energy, binding energy, core-core interaction, bond lengths, and the charge on sulfur atom were calculated (Table 1).

The results of Table 1 show that thiol **3e** has the highest charge on sulfur atom (0.144) and a minimal C-S length (1.757 Å).

Evaluation of antimicrobial activity. Biological screening of antimicrobial activity of synthesized thiols was carried out. Data of Table 2 present the inhibition zones (mm) of thiols **3d,e,h-l,n**, DCNQ, oxacillin and DMF (solvent) determined for *Escherichia coli* and *Staphylococcus aureus*. Gram positive strain *St.aureus* showed inhibition zone ranging from 13 to 45 mm, *E.coli* — from 15 to 30 mm, respectively.

Therefore, thiols **3d,e,h-l,n** were active against Gram-negative and Gram-positive strains. The results of antimicrobial activity indicated that **3e,h** has greater activity than oxacillin and DCNQ. The determination of minimal bacteriostatic and minimal bactericidic concentrations (MBSC and MBCC) of thiols **3k,l,n** for *Escherichia coli*, *Staphylococcus aureus* and *Mycobacterium luteum* using serial dilution [22] is shown in Table 3.

Therefore, antimicrobial activity of 2-substi-

Table 1

*Selected molecular parameters of thiols **3d,e,h-l,n** as calculated by semi-empirical method PM3*

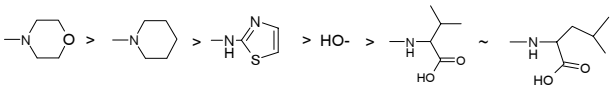
Thiol	Charge on sulfur	C-S length, Å	Total Energy, kcal/mol	Electronic Energy, kcal/mol	Binding Energy, kcal/mol	Core-Core Interaction, kcal/mol
3d	0.139	1.759	-67872.44	-476441.53	-3663.77	408569.09
3e	0.144	1.757	-71187.42	-481462.22	-3474.26	410274.80
3h	0.109	1.773	-67906.20	-433120.77	-3072.64	365214.57
3k	0.086	1.769	-54033.52	-285608.62	-2325.73	231575.09
3l	0.099	1.758	-84883.37	-613639.10	-4161.63	528755.73
3n	0.092	1.759	-81434.84	-572397.40	-3881.14	490962.55

Table 2

Antimicrobial activity of thiols ***3d,e,h-l,n*** *as determined by diffusion techniques*

Microorganism	Gram	Inhibition zone (mm)								
		3d	**3e**	**3h**	**3k**	**3l**	**3n**	DMF	DCNQ	oxacillin
Escherichia coli	-	30	30	20	15	18	16	0	17	0
Staphylococcus aureus	+	23	45	19	15	15	13	24	20	24

tuted-3-mercapto-1,4-naphthoquinones **3d,e,h-l,n** decreases in following order of substituents:



Greater activity of 2-morfolino-3-mercapto-1,4-naphthoquinone **3e** can probably be explained by higher charge on sulfur atom (0.144) and the smallest length of C-S bond (1.757 Å) in comparison with other thiols (Table 1). Structure of this thiol is shown in Fig. 1.

Prediction of the structure for thiols **3d,e,h-l,n** was estimated on the basis of their structural formula with computer program *PASS C&T* (Prediction of Activity Spectra for Substances) [23, 24]. In the «Prediction Results» you obtain the total number of chemical descriptions of your compound, and the number of descriptors which are new comparing to the descriptors in 30.900 compounds from the PASS training set. The result of prediction is presented as the list of activities with appropriate Pa, which estimates the probability for the compound to be active and inactive respectively for each type of activity from the biological activity spectrum. Its values vary from 0.000 to 1.000. If Pa>0.7 the compound is very likely to reveal this activity in experiments, but in this case the chance of being the analogue of the known pharmaceutical agents for this compound is also high. If 0.5<Pa<0.7 the compound is likely to reveal this activity in experiments, but this probability is less, and the compound is not so similar to the known pharmaceutical agents. If Pa<0.5 the compound is unlikely to reveal this activity in experiments, but if the presence of this activity is confirmed in the experiment the compound might be a New Chemical Entity.

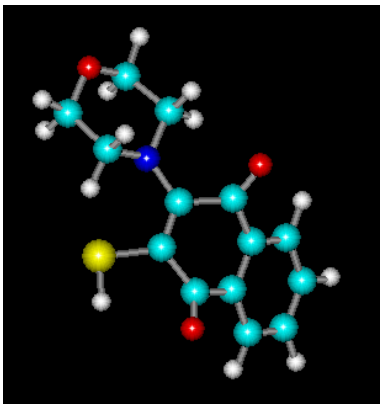


Fig. 2. Structure of thiol ***3e****.*

The results of Table 4 show that **3e,d,k** have a wide spectrum prediction and appropriate Pa for **3k** approaches 1. It is possible to expect higher probability of antiviral, antiinflammatory, antiallergic, antipruritic activity for the represented compounds.

Data of antimicrobial activity, PASS prediction and quantum-chemistry calculations by PM3 were the base for determination of «structure — activity» correlation (Fig. 2-4).

Conclusion. Therefore, the preparative method of synthesis of new thiols on the base of 2-substituted-3-mercapto-1,4-naphthoquinones. Synthesized compounds with a high antimicrobial activity against *St.aureus* and *E.coli* were found among them. Previous computer screening indicates the necessity of further investigation was described compounds of this class.

Table 3

Minimal inhibition concentrations for thiols ***3k,l,n***

Thiol	Microorganisms					
	St.aureus		*E.coli*		*M.lutenum*	
	MBSC, μg/ml	MBCC, μg/ml	MBSC, μg/ml	MBCC, μg/ml	MBSC, μg/ml	MBCC, μg/ml
3k	64	160	160	1000	16	32
3l	64	160	400	1000	32	64
3n	160	400	400	1000	64	160

Table 4

The results of prediction with Pa>0.7 for thiols ***3d,e,h-l,n***

Thiol	Pa	Activity Name
3d	0.877	Peptide deformylase inhibitor
	0.805	Gentisate 1,2-dioxygenase inhibitor
	0.775	Lysase inhibitor
	0.763	Quercetin 2,3-dioxygenase inhibitor
	0.752	2-Nitropropane dioxygenase inhibitor
	0.761	Dopamine D4 agonist
	0.749	Styrene-oxide isomerase inhibitor
	0.725	Magnesium-protoporphyrin IX monomethyl ester cyclase inhibitor
	0.712	Catechol oxidase inhibitor
	0.720	NAD(P)+-arginine ADP-ribosyltransferase inhibitor
3e	0.853	Peptide deformylase inhibitor
	0.790	Gentisate 1,2-dioxygenase inhibitor
	0.766	Quercetin 2,3-dioxygenase inhibitor
	0.769	Lysase inhibitor
	0.768	Styrene-oxide isomerase inhibitor
	0.715	2-Nitropropane dioxygenase inhibitor
	0.727	Arylacetonitrilase inhibitor
	0.706	Laccase inhibitor
	0.718	NAD(P)+-arginine ADP-ribosyltransferase inhibitor
3h	0.786	Peptide deformylase inhibitor
	0.720	Gentisate 1,2-dioxygenase inhibitor
	0.719	Lysase inhibitor
3k	0.977	Arylacetonitrilase inhibitor
	0.975	Gentisate 1,2-dioxygenase inhibitor
	0.975	2-Nitropropane dioxygenase inhibitor
	0.955	2,5-Dihydroxypyridine 5,6-dioxygenase inhibitor
	0.954	Catechol 1,2-dioxygenase inhibitor
	0.954	Ferredoxin hydrogenase inhibitor
	0.940	Peroxidase inhibitor
	0.922	Peptide deformylase inhibitor
	0.914	Quercetin 2,3-dioxygenase inhibitor
	0.888	NAD(P)+-arginine ADP-ribosyltransferase inhibitor
	0.881	Styrene-oxide isomerase inhibitor
	0.873	Hyoscyamine (6S)-dioxygenase inhibitor
	0.843	Magnesium-protoporphyrin IX monomethyl ester cyclase inhibitor
	0.834	Catechol oxidase inhibitor
	0.827	Quinoprotein glucose dehydrogenase inhibitor
	0.808	Lysase inhibitor
	0.799	Laccase inhibitor
	0.780	Nitrile hydratase inhibitor
	0.757	3-Hydroxybenzoate 4-monooxygenase inhibitor
	0.799	Membrane integrity agonist
	0.746	Trans-cinnamate 4-monooxygenase inhibitor
	0.758	Leucolysin inhibitor
	0.798	Antiseborrheic
	0.748	D-xylulose reductase inhibitor
	0.716	Catechol 2,3-dioxygenase inhibitor
	0.728	Pectate lyase inhibitor
	0.757	Monodehydroascorbate reductase (NADH) inhibitor
3l	0.824	Peptide deformylase inhibitor
	0.807	Peptidyl-dipeptidase Dcp inhibitor
	0.783	Coccolysin inhibitor
	0.791	Pitrilysin inhibitor
	0.737	Leucolysin inhibitor
	0.731	D-xylulose reductase inhibitor
	0.725	Styrene-oxide isomerase inhibitor
3n	0.834	Peptide deformylase inhibitor
	0.832	Leucolysin inhibitor
	0.808	D-xylulose reductase inhibitor
	0.795	2-Nitropropane dioxygenase inhibitor
	0.807	Styrene-oxide isomerase inhibitor
	0.790	Aldose-6-phosphate reductase (NADPH) inhibitor
	0.780	Gentisate 1,2-dioxygenase inhibitor
	0.790	Lysase inhibitor

Table 5

Data of the synthesized compounds

Thiol	Formula, mp °C / yield, %	^{1}H NMR (δ, ppm)	IR, cm^{-1}	Calculated Found, %			
				C	H	S	N
3h	$C_{13}H_8S_2N_2O_2$, 178-180 / 72	8.49 (1H, s, NH); 8.07-8.18 (2H, dd, CH_{Ar}); 7.71-7.82 (2H, dd, CH_{Ar}); 7.17 (1H, d, CH=); 6.68 (1H, d, CH=); 3.61 (1H, s, SH)	3610 (OH); 3360 (NH); 2550 (SH); 1660 (C=O)	54.15 54.49	2.80 2.63	22.24 22.39	9.72 9.65
3l	$C_{16}H_{17}SNO_3$ 113-115 / 69	9.41 (1H, s, OH); 7.78; 7.71 (2H, td, CH_{Ar}), 8.47 (1H, s, CH); 8.15; 8.01 (2H, dd, CH_{Ar}); 7.61 (1H, s, NH); 3.68-3.69 (2H, m, N-CH_2); 2.04-2.08 (1H, m, CH); 1.05-1.08 (6H, m, $2CH_3$)	3620 (OH); 3375 (NH); 2537 (SH); 1627 (C=O)	63.35 63.65	5.65 5.41	10.57 10.73	4.62 4.48
3m	$C_{15}H_{15}SNO_3$ 128-129 / 68	9.47 (1H, s, OH); 8.54 (1H, s, CH); 7.69; 7.51 (2H, td, CH_{Ar}), 7.92; 7.82 (2H, dd, CH_{Ar}); 7.64 (1H, s, NH); 4.30-4.41 (2H, m, N-CH); 2.06-2.10 (1H, m, CH); 1.13-1.19 (3H, s, CH_3)	3634 (OH); 3140 (NH); 2530 (SH); 1642 (C=O)	62.26 62.51	5.23 5.45	11.08 11.21	4.84 4.72
3n	$C_{13}H_{11}SNO_3$ 146-148 / 71	9.35 (1H, s, OH); 8.7 (1H, s, CH); 7.62; 7.53 (2H, td, CH_{Ar}), 7.89; 7.68 (2H, dd, CH_{Ar}); 7.54 (1H, s, NH); 3.83-3.92 (2H, m, N-CH); 2.06-2.10 (1H, m, CH); 0.99-1.03 (6H, m, $2CH_3$)	3590 (OH); 3328 (NH); 2548 (SH); 1658 (C=O)	59.76 59.92	4.24 4.12	12.27 12.45	5.36 5.47
3o	$C_{19}H_{15}SNO_4$ 180-181 / 73	8.25 (1H, s, OH); 8.08-8.11 (2H, m, CH_{Ar}); 7.83 (1H, m, CH_{Ar}); 7.55 (1H, m, CH_{Ar}); 7.24 (1H, m, CH=); 6.94 (2H, m, CH=); 6.85 (1H, s, NH); 4.69 (1H, q, CH); 3.52 (1H, s, SH); 3.21-3.46 (2H, m, CH_2)	3618 (OH); 3354 (NH); 2537 (SH); 1665 (C=O)	64.58 64.69	4.28 4.13	9.07 9.15	3.96 4.03

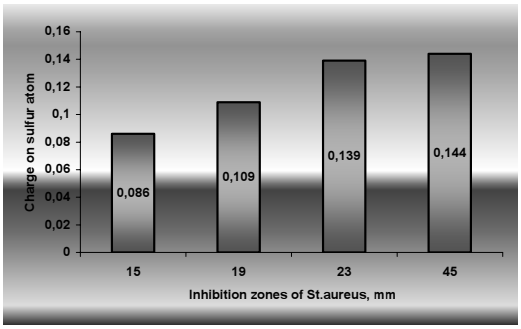


Fig. 2. The correlation «antimicrobial activity — charge» for thiols ***3d,e,h,k****.*

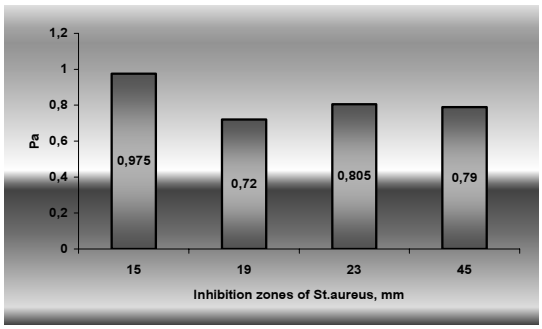


Fig. 3. The correlation «antimicrobial activity — Pa» for thiols* ***3d,e,h,k.***

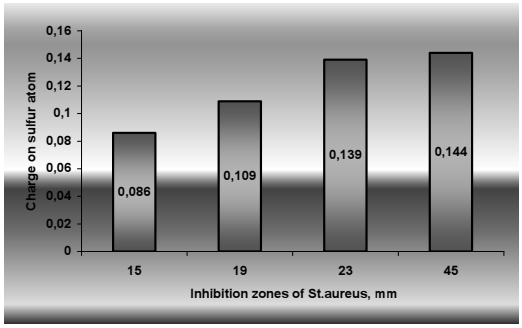


Fig. 4. The correlation «Pa — charge» for thiols* ***3d,e,h,k.***

Pa — Pa value for Gentisate 1,2-dioxygenase inhibitor (as example).*

Experimental. Melting points were measured on a Nagema melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Varian VXR (300 MHz) spectrometer in DMSO-d_6 with TMS as an internal standard. IR spectra were recorded on Specord M75 in KBr tablets.

2-Substituted-3-mercapto-1,4-naphthoquinones 3a-g, k [14].

Synthesis of 2-substituted-3-mercapto-1,4-naphthoquinones 3h,l-o. 0.016 mol of sodium sulfide was added to 0.015 mol of 2-R-3-mercapto-1,4-naphthoquinone in 70 ml of DMF. Reaction mixture was warmed up at 45-50 °C for 3 hr, filtered, then cooled. To reaction mixture added 500 ml of aqua and 50 ml of 10 % HCl, crystals of thiol dropped of it which was washed by water and dried, crystallized from EtOH-DMF (1:2). Data of the synthesized compounds are shown in Table 5.

Microbial culture growth conditions. Tested microorganisms included the following bacteria: *Staphylococcus aureus* and *Escherichia coli.* All bacteria were grown at 37 °C in medium with peptone yeast extract. Disks (5 mm diameter) were soaked in 0.02 mg mL^{-1} of thiols solutions in DMF. Disks were put on an exponentially growing plated culture with appropriate dilution to 1.0×10^6 colony forming unit. The plates were then incubated for 24 hr at 37 °C. The results were recorded by measuring the zones surrounding the disk. Control disks contained DMF, DCNQ and oxacillin.

Надійшла до редакції 30.06.2006 р.

Синтез та антимікробні дослідження нових 2-заміщених-3-тіол-1,4-нафтохінонів

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Резюме. Синтезовано ряд 2-заміщених-3-тіол-1,4-нафтохінонів, досліджено їх антимікробну активність. Подано методику синтезу, спектроскопічні дані та дані антимікробної активності. 2-Морфоліно-3-тіол-1,4-нафтохінон та 2-піперидино-3-тіол-1,4-нафтохінон показали вищу антимікробну активність, ніж відомий антибіотик оксацилін. Квантово-хімічні розрахунки виконувалися з використанням напівемпіричного методу PM3 для встановлення геометрії молекул та електронної структури одержаних тіолів. Проведений прогноз біологічної активності з використанням комп'ютерної програми *PASS C&T* показав доцільність подальших досліджень нових синтезованих сполук.

Ключові слова: тіол, нафтохінон, антимікробна активність, *PASS C&T*.

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