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SYNTHESIS OF NEW 1,5-SUBSTITUTED TETRAZOLES BASED ON *N*-BENZOYL-*N'*-(9,10-DIOXO-9,10-DIHYDRO-ANTHRACENYL) THIOUREAS

Одержано нові 1,5-заміщені тетразольні похідні взаємодією раніше одержаних *N*-бензоїл-*N'*-(9,10-діоксо-9,10-дигідроантрацен-1-іл) тіосечовин з азидом натрію при кімнатній температурі в ДМФА і в присутності триетиламіну та молекулярного йоду. Запропоновано можливий механізм утворення [(1-бензоїл-1*H*-тетразол-5-іл) аміно] антрацен-9,10-діонів. Проведено комп'ютерній скринінг програмою PASS Online, який показав перспективні напрямки експериментальних досліджень синтезованих сполук.

Ключові слові: бензоїлтіосечовина; 9,10-антрахінон; азид натрію; йод; тетразол.

New 1,5-substituted tetrazole derivatives were obtained by reaction of early synthesized *N*-benzoyl-*N'*-(9,10-dioxo-9,10-dihydroantracene-1-yl) thioureas with sodium azide at room temperature in DMF and presence of triethylamine and molecular iodine. The plausible mechanism of formation of [(1-benzoyl-1H-tetrazole-5-yl) amino] anthracene-9,10-diones was proposed. A computer screening by program PASS Online, which showed promising areas of experimental studies of the synthesized compounds, was carried out.

Keywords: benzoylthiourea; 9,10-anthraquinone; sodium azide; iodine; tetrazole.

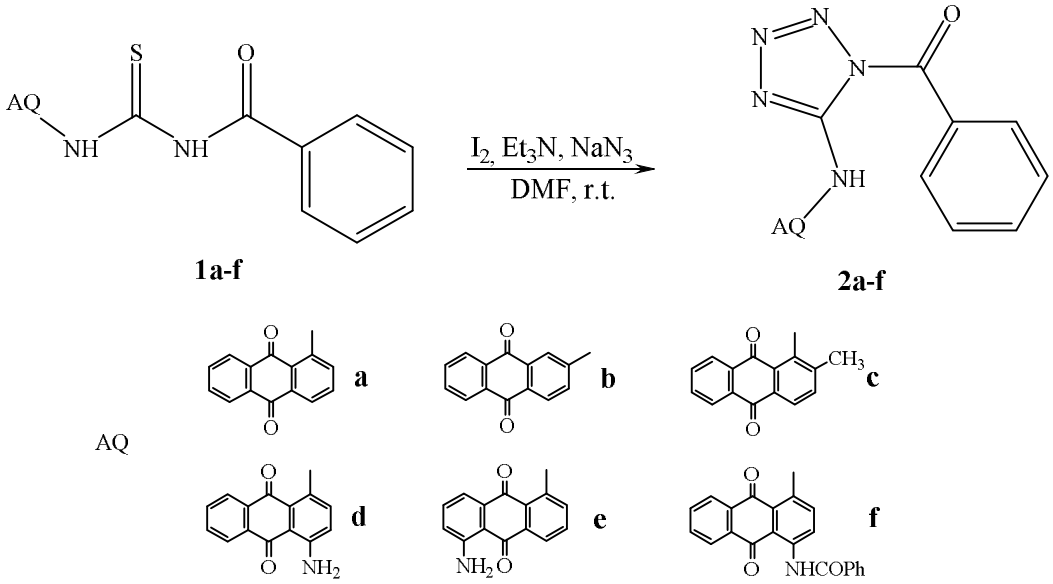
Introduction. It is known that N-aroylthiourea are marked as substances with a powerful synthetic potential. They are important reagents for the synthesis of several heterocycles, such as imidazolidinyl-2-thiones [1], 2-aroyliminothiazolines [2], 1,2,4-triazoles [3], 1,3-thiazines [4] and indeno [1,2-d][1,3] thiazepines [5]. 2-Iminothiazolines characterized by a wide spectrum of biological properties [6]. Thiazoliden-2-imine [7], thiazole-2-imine [8] and 2-iminothiazole [9] fragments are present in candidate substances for drugs with a wide complex of action: muscarinomimetic, antifungal, hypolipemic, anti-diabetic, anti-inflammatory, cardiotonic and bactericidal [10]. Tetrazole and his derivatives are attracts attention due to its unique structure and ability to serve as bioequivalent (bioisostere) to carboxyl group and using as an antihypertensive, anti-allergic, antibiotic and anticonvulsant drugs, etc. [11–18].

In literature are missing information about 1,5-tetrazole systems based on 9,10-anthracenedione. Taking into account expressed biological properties of anthraquinone derivatives [19–21], it seems appropriate to design hybrid structures, which include antraquinonic and tetrazole cycles.

Aim. The synthesis of new derivatives of 9,10-anthraquinone with tetrazole fragment and *in silico* screening of probable biological action to identify further areas of experimental studies of these compounds.

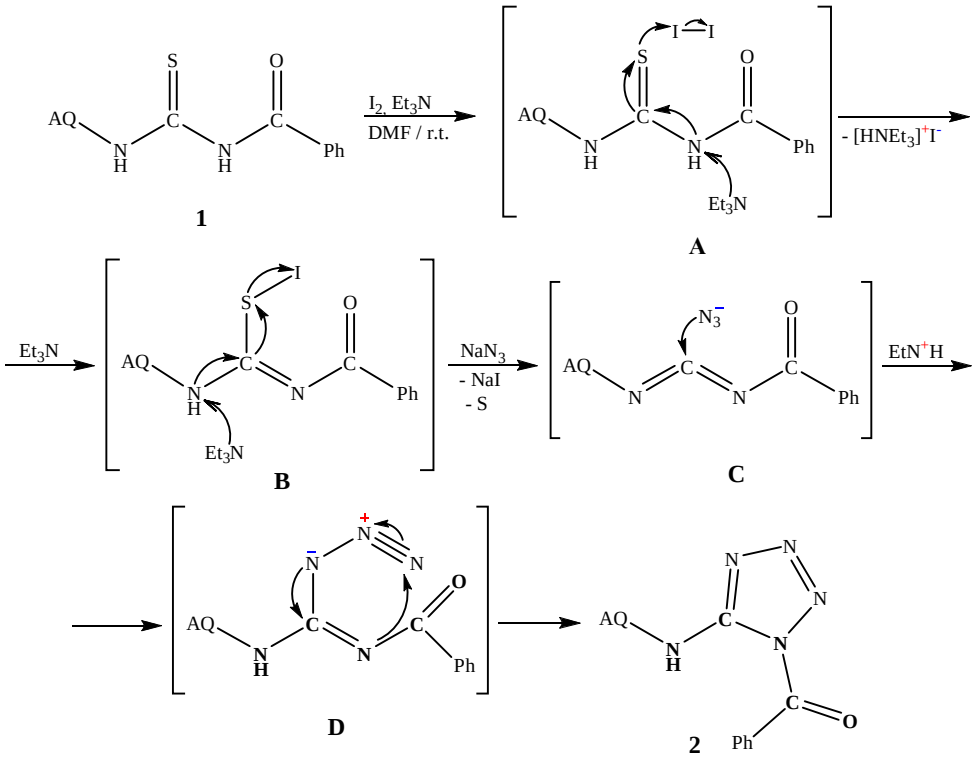
Scientific novelty of the obtained results. In first time the new promising bioactive compounds were obtained with include in its structure two known pharmacophore fragments – antraquinone and tetrazole.

Discussion of results. For obtaining of tetrazoles from *N,N'*-disubstituted thioureas is known to use different desulfurization agents such as plumbum and mercury salts [22]. However, in recent years, molecular iodine is widely used as a catalyst in many transformations due to its cheapness, nontoxic, accessibility and easy to separation from reaction systems [22]. Therefore, we have performed interaction of *N*-benzoyl-*N*'-(9,10-dioxo-9,10-dihydroanthracenyl) thioureas **1a-f** [23] and sodium azide (Scheme 1) under room temperature in DMF and presence triethylamine and molecular iodine with obtaining of [(1-benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-diones **2a-f** according to optimized methodology in [22]:



Scheme 1. Obtaining of [(1-benzoyl-1H-tetrazole-5-yl) amino] anthracen-9,10-diones ***2a-f***

Probable mechanism of formation of [(1-benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-diones **2a-f** likely occur according to the scheme 2:



Scheme 2. Probable mechanism of formation of 1,5-substituted tetrazoles ***2a-f*** *based on N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracen-1-yl) thioureas* ***1a-f***

At the first stage occurs initial attack of triethylamine on more acidic proton of secondary amino group of benzoylthioureyl substituent, at the same time molecular iodine is attacking on sulfur atom of thiourea by with forming of intermediate **A**. The next stage includes elimination of [$HNEt_3$] I molecule and next attack of triethylamine on second hydrogen of secondary amino group with simultaneous desulfurization (intermediate **B**). Result of the second stage is obtaining of carbodiimide intermediate **C**, where occurs the attack by azide anion on electrophilic carbon atom of carbodiimide fragment, protonation of less acidic imide proton of thioureyl substituent and next intramolecular cyclization (intermediate **D**) with obtaining of tetrazole **2**.

Formation of tetrazoles **2a-f** are confirmed by ^{1}H NMR spectra and chromatography-mass spectrometry. In ^{1}H NMR spectra of synthesized compounds is present signal only for one hydrogen atom of secondary amino group within 12.32-13.72 ppm. In chromatography-mass spectra are present peaks of corresponding molecular ions of target products **2a-f**.

For obtained tetrazoles **2a-f** was carried out *in silico* screening using software PASS Online [24] (Pa>0.5), which has shown prospects of experimental research, primarily on such types of activity as antibacterial, antifungal, antiasthmatic, anti-allergic, anti-tumor, etc.

The combined results of the *in silico* screening of plausible range of biological activity are presented in Table.

Predicted biological activity of tetrazole derivatives 2a-f on condition P_a>0.5

Compound / Activity	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**
3-Hydroxybenzoate 6-monooxygenase inhibitor	0.824	0.760	0.760	0.691	0.691	0.599
Antineoplastic	0.534	0.567	0.567	-	-	-
Indanol dehydrogenase inhibitor	0.518	-	-	-	-	-
4-Hydroxyphenylacetate 3-monooxygenase inhibitor	0.501	-	-	0.507	0.507	-
Histamine release inhibitor	0.509	0.519	0.519	-	-	-
Pterin deaminase inhibitor	0.508	0.508	0.508	-	-	-
5 Hydroxytryptamine release inhibitor	-	0.514	0.514	-	-	0.501
Membrane permeability inhibitor	-	0.562	0.562	-	-	-

Experimental part. ^{1}H NMR spectra were obtained on the device Varian Mercury-400 (399.9601 MHz) in solutions of DMSO-d_6, internal standard TMS. Chromatography-mass spectra were recorded on the device Agilent 110\DAD\HSD\VLG 119562.

[(1-Benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-diones 2a-f (General methodology). To corresponding benzoyl-*N'*-(9,10-dioxo-9,10-dihydroanthracen-1-yl) thiourea **1a-f** (1.294 mmol) in 30 ml of DMF were added molecular iodine (0.361 g, 1.423 mmol), sodium azide (0.252 g, 3.882 mmol) and triethylamine (0.393 g, 3.882 mmol), after which the reaction mixture stirred at room temperature during 6 h. Than reaction mixture was filtered from sulfur, to filtrate added 150 ml of water. The precipitate was filtered and dried in a vacuum. The product was purified using a chromatographic column, eluent benzene:acetonitrile (6:1).

1-[(1-Benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-dione 2a. Yield 58 %. Mp. = = 276–278 ^{0}C. ^{1}H NMR spectrum, δ ppm: 7.55–7.67 m (4H, CH_{ar}); 7.86-7.93 м (3H, CH_{ar}); 8.12-8.21 m (4H, CH_{ar}); 8.51 d (1H, *J*=7.7 *Hz*, CH_{ar}); 13.34 с (1H, NH). Chromatography-mass spectrum, *m/z* (I_{rel}., %): 396 [M+1] (99.2). Found, %: C 66.96; H 3.23; N 17.62. $C_{22}H_{13}N_5O_3$. Calculated, %: C 66.83; H 3.31; N 17.71.

2-[(1-Benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-dione 2b. Yield 63 %. Mp. = 254-255 ^{0}C. ^{1}H NMR spectrum, δ ppm: 7.53–7.68 м (3H, CH_{ar}); 7.92–8.01 m (4H, CH_{ar}); 8.19–8.22 m (4H, CH_{ar}); 8.71 s (1H, CH_{ar}); 12.81 s (1H, NH). Chromatography-mass spectrum, *m/z* (I_{rel}., %): 396 [M+1] (97.9). Found, %: C 66.89; H 3.27; N 17.78. $C_{22}H_{13}N_5O_3$. Calculated, %: C 66.83; H 3.31; N 17.71.

1-[(1-benzoyl-1*H*-tetrazole-5-yl) amino]-2-methylanthracen-9,10-dione 4c. Yield 60 %. Mp. = 277–278 ^{0}C. ^{1}H NMR spectrum, δ ppm: 2.41 c (3H, CH_3); 7.56–7.64 m (2H, CH_{ar}); 7.67–7.71 m (1H, CH_{ar}); 7.83–7.92 m (3H, CH_{ar}); 8.04–8.16 m (5H, CH_{ar}); 12.32 s (1H, NH). Chromatography-mass spectrum, *m/z* (I_{rel}., %): 410 [M+1] (98.9). Found, %: C 67.54; H 3.73; N 17.02. $C_{23}H_{15}N_5O_3$. Calculated, %: C 67.48; H 3.69; N 17.11.

1-Amino-4-[(1-benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-dione 2d. Yield 62 %. Mp. = 265–266 ^{0}C. ^{1}H NMR spectrum, δ ppm: 7.19 d (1H, *J*=8.3 *Hz*, CH_{ar}); 7.55–7.67 m (4H, CH_{ar}, NH_2); 7.84–8.19 m (8H, CH_{ar}); 13.44 s (1H, NH). Chromatography-mass spectrum, *m/z* (I_{rel}., %): 411 [M+1] (98.8). Found, %: C 64.45; H 3.51; N 20.39. $C_{22}H_{14}N_6O_3$. Calculated, %: C 64.39; H 3.44; N 20.48.

1-Amino-5-[(1-benzoyl-1*H*-tetrazole-5-yl) amino] anthracen-9,10-dione 2e. Yield 63 %. Mp. = 241–242 ^{0}C. ^{1}H NMR spectrum, δ ppm: 7.12 d (1H, *J*=7.9 *Hz*, CH_{ar}); 7.19–7.21 m (2H, CH_{ar}); 7.38–7.61 m (4H, CH_{ar}, NH_2); 7.69–8.09 m (3H, CH_{ar}); 8.13 d (1H, *J*=7.7 *Hz*, CH_{ar}); 8.71 d (1H, *J*=8.0 *Hz*, CH_{ar}); 13.72 s (1H, NH). Chromatography-mass spectrum, *m/z* (I_{rel}., %): 411 [M+1] (99.2). Found, %: C 64.42; H 3.38; N 20.52. $C_{22}H_{14}N_6O_3$. Calculated, %: C 64.39; H 3.44; N 20.48.

***N*-[4-((1-Benzoyl-1*H*-tetrazole-5-yl) amino)-9,10-dioxo-9,10-dihydroanthracen-1-yl) benzamide 2f.** Yield 65 %. Mp. = 281–482 ^{0}C. ^{1}H NMR spectrum, δ ppm: 7.39 d (1H, *J*=8.1 *Hz*, CH_{ar}); 7.53–7.69 m (6H, CH_{ar}); 7.71–7.91 m (5H, CH_{ar}); 8.17–8.23 m (4H, CH_{ar}); 8.90 s (1H, NH); 13.35 s (1H, NH). Chromatography-mass spectrum, *m/z* (I_{rel}., %): 515 [M+1] (100). Found, %: C 67.77; H 3.63; N 16.27. $C_{29}H_{18}N_6O_4$. Calculated, %: C 67.70; H 3.53; N 16.33.

Conclusions. As a result of this work new 1,5-substituted tetrazole derivatives by interaction of *N*-benzoyl-*N*'-(9,10-dioxo-9,10-dihydro-anthraceneyl) thioureas with sodium azide at room temperature in DMF in the presence of molecular iodine as desulfurization agent and catalyst were synthesized. The plausible mechanism of formation of [(1-benzoyl-1H-tetrazole-5-yl) amino] anthracene-9,10-diones was proposed. *In silico* screening by program PASS Online showed promising areas of experimental studies of new tetrazole derivatives based on 9,10-anthraquinone, in particular antibacterial, antifungal, antiasthmatic, anti-allergic and anti-tumor activities

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