ISSN 1392 – 1231. CHEMINĖ TECHNOLOGIJA. 2013. Nr. 2 (64)

Computer prediction and synthesis of new azoles based on N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracen-1-yl)thioureas

V. Zvarych, M. Stasevych, O. Stanko, V. Novikov
Lviv Polytechnic National University,
79013, Lviv-13, S. Bandera Str. 12, Ukraine
E-mail vnovikov@polynet.lviv.ua

M. Vovk
Institute of Organic Chemistry of NASU,
02660, Kyiv-94, Murmanska Str. 5, Ukraine

V. Poroikov
Orekhovich Institute of Biomedical Chemistry of Russian Academy of Medical Sciences,
119121, Moscow, Pogodinskaya Str. 10/8, Russia

O. Solovyov
Shupyk National Medical Academy of Postgraduate Education,
04112, Kyiv, Dorohozhyts'ka Str. 9, Ukraine

crossref http://dx.doi.org/10.5755/j01.ct.64.2.6018

Received 27 November 2013; Accepted 12 December 2013

New thiazole and 1,2,4-triazole derivatives of 9,10-anthraquinone were obtained by the reaction of N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracene-1-yl)-thioureas with bromoacetone in the presence of triethylamine and hydrazine hydrate in chloroform, respectively. The PASS computer program was used to predict the biological activity spectra and to determine the most promising biological activities for experimental testing. Thus, it has been shown that the synthesized compounds are a promising class for the creation of substances with a wide range of biological activity.

Keywords: 9,10-anthraquinones, benzoylthioureas, cyclization, thiazol-2-imines, 1,2,4-triazoles

Introduction

The possibility of obtaining a large number of in practical terms valuable substances based on 9,10-anthraquinone derivatives is in accordance with the most important area of synthetic organic chemistry – the targeted synthesis of new organic compounds possessing a specified set of chemical, physical, and biological properties. An increasing number of publications about the synthesis and application of 9,10-anthraquinone derivatives testifies a continued interest in this series of compounds worldwide. Despite the widely studied chemistry of 9,10-anthraquinone, many classes of 9,10-anthraquinone derivatives remain scarcely explored.

On the other hand, N-aroylthioureas have a strong synthetic potential. They are important reagents for the synthesis of several heterocycles, such as imidazolidinyl-2-thiones [1, 2], 2-aroyliminothiazolines [3–5], 1,2,4-triazoles [6], 1,3-thiazines [7] and indeno[1,2-d][1,3]thiazepines [8]. 2-Iminothiazolines are characterized by a wide range of biological properties [9–12]. The thiazolidene-2-imine [13] or thiazol-2-imine [14] or 2-iminothiazoline[15–18] ring system, as it has been named by different groups, is present in several drug candidates possessing interesting biological activities such as muscarinomimetic, antimycotic, hypolipemic, antidiabetic, thrombopoietinagonism, cell adhesion antagonists, platelet GPIIb/IIIa receptorantagonists, anti-inflammatory, analgesic and kinase (CDK1, CDK5 and GSK3) inhibition, schistosomicides, cadiotonicsand trichomonides [19–23]. Thiazoline derivatives have been found to exhibit promising applications in agriculture, such as acaricides, insecticides, and plant growth regulators [24, 25]. Recently, 2-iminothiazolines have been found to show antifungal activity [26] and skin whitening action [27].

The 1*H*-1,2,4-triazole compounds show important pharmacological activities, e. g., antifungal and antiviral. Examples of such compounds bearing the 1,2,4-triazole residues are fluconazole [28] and ribavirin, the powerful azole antifungal agent as well as the potent antiviral *N*-nucleoside [29]. Furthermore, various 1,2,4-triazole derivatives have been reported as fungicidal [30], insecticidal [31], and antimicrobial [32] agents. Some of them have shown antitumor activity [33, 34]; anticonvulsants [35], antidepressants [36], plant growth regulators, and anticoagulants [37] have been identified among them as well.

The reaction of N,N'-disubstituted thioureas with α-bromketones [5, 13] allows obtaining a variety of N-substituted 2-iminothiazoles. However, their derivatives that contain 9,10-dioxo-9,10-dihydroanthracenyl fragments at the 3rd position of the heterocycle remain unknown up to date. 1,2,4-Triazole derivatives of 9,10-anthraquinone are

also not described in the literature. Taking into account the known biological properties of anthraquinone derivatives [38–40], it seems appropriate to design hybrid structures containing anthraquinone and thiazole or triazole cycles.

Materials and methods

^{1}H NMR and ^{13}C spectra were recorded with a Varian Mercury-400 spectrometer (400 and 100 MHz, respectively) at 25 °C in DMSO-d_6, using TMS as an internal standard. IR spectra were obtained on a Specord M80 spectrophotometer, using KBr tablets. Chromato-mass spectra were recorded on Agilent 110\DAD\HSD\VLG 119562 device. Melting points were determined with an automatic APA1 melting point apparatus and are uncorrected.

N-[3-(R^1,R^2,R^3)-9,10-Dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3*H*)-ylidene]benzamide 2 a–e (general method). To a stirred suspension of 0.749 mmol of N-benzoylthiourea **1 a–e** and of 0.104 ml (0.749 mmol) of triethylamine in 30 ml of acetone, at stirring, the solution of 0.0384 ml (0.749 mmol) of bromine in 10 ml of acetone was added over 10 min. The reaction mixture was kept at room temperature for 2 h, the precipitate formed was filtered, washed with acetone and water, dried, and recrystallized from toluene.

N-(3-(9,10-Dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3*H*)-ylidene)benzamide (2 a).

Yield 68 %, Mp. 210–211 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 1.99 (3H, s, CH_3); 6.92 (1H, s, CH=); 6.98 (3H, m, H Ar); 7.68–7.70 (3H, m, H Ph); 7.99 (2H, m, H Ph); 8.21 (3H, m, H Ar); 8.53 (1H, d, *J* = 8.4, H Ar).

^{13}C NMR, δ, ppm: 14.2 (CH_3CH=); 106.7 (CH=); 126.8, 127.3, 127.5, 128.4 (C Ar); 128.7, 129.1, 129.3, 129.1 (C Ph); 131.5 (C Ar); 132.4 (C Ph); 133.5, 133.6, 134.4, 134.9, 135.2 (C Ar); 135.8 (C Ph); 137.8 (C-N); 143.3 (CH_3CH=); 168.5 (C=N); 173.5 (COPh); 181.8 (CO); 182.5 (CO).

IR spectra, ν, cm^{-1}: 1680, 1631 (C=O quinone ring), 1685 (COPh), 1471 (C=N).

Chromato-mass spectra, *m/z* (I_{rel}, %): 425 $[M+H]^+$ (69).

Found, %: C 70.61; H 4.01; N 6.71; S 7.79. $C_{25}H_{16}N_2O_3S$.

Calculated, %: C 70.74; H 3.80; N 6.60; S 7.55.

N-(4-Methyl-3-(2-methyl-9,10-dioxo-9,10-dihydro-anthracen-1-yl)thiazol-2(3*H*)-ylidene)benzamide (2 b).

Yield 51 %, Mp. 206 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 1.99 (3H, s, CH_3); 2.17 (3H, s, CH_3); 7.01 (1H, s, CH=); 7.24–7.27 (2H, m, H Ph); 7.36 (1H, m, H Ph); 7.72 (2H, m, H Ph); 7.85–7.90 (2H, m, H Ar); 8.02 (1H, d, *J* = 7.5, H Ar); 8.14 (1H, d, *J* = 7.5, H Ar); 8.21 (1H, d, *J* = 7.5, H Ar); 8.44 (1H, d, *J* = 7.6, H Ar).

^{13}C NMR, δ, ppm: 13.9 (CH_3CH=); 17.7 (CH_3); 106.1 (CH=); 126.8, 127.3, 127.6, 128.5 (C Ar); 128.8, 128.9, 129.0, 129.1 (C Ph); 131.8 (C Ar); 132.8 (C Ph); 133.7, 133.9, 134.0, 135.0, 135.1 (C Ar); 135.2 (C Ph); 137.1 (C Ar); 137.3 (C-N); 144.9 (CH_3CH=); 168.7 (C=N); 173.1 (COPh); 182.1 (CO); 182.4 (CO).

IR spectra, ν, cm^{-1}: 1681, 1623 (C=O quinone ring), 1670 (COPh), 1397 (C=N).

Chromato-mass spectra, *m/z* (I_{rel}, %): 439 $[M+H]^+$ (97).

Found, %: C 71.61; H 4.01; N 6.71; S 7.79. $C_{26}H_{18}N_2O_3S$.

Calculated, %: C 71.22; H 4.14; N 6.39; S 7.51.

N-(3-(4-Amino-9,10-dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3*H*)-ylidene)benzamide (2 c).

Yield 50 %, Mp. 296–297 °C. ^{1}H NMR, δ, ppm (*J*, Hz): 1.98 (3H, s, CH_3); 6.89 (1H, s, CH=); 7.26 (3H, m, H Ar, NH_2); 7.38–7.41 (2H, m, H Ar); 7.49–7.57 (3H, m, H Ph); 7.68–7.73 (2H, m, H Ph); 7.87–7.91 (2H, m, H Ar); 8.23 (1H, d, *J* = 7.6, H Ar).

^{13}C NMR, δ, ppm: 13.7 (CH_3CH=); 107.2 (CH=); 114.5, 125.3, 126.1, 127.2 (C Ar); 128.1, 128.2, 129.3, 129.4 (C Ph); 130.1 (C-N); 130.9, 131.3 (C Ar); 132.3 (C Ph); 133.1, 133.2, 133.5, 133.8 (C Ar); 136.1 (C Ph); 139.8 (CH_3CH=); 147.8 (C-NH_2); 169.7 (C=N); 174.5 (COPh); 183.1 (CO); 184.3 (CO).

IR spectra, ν, cm^{-1}: 3365 (NH_2), 1683, 1625 (C=O quinone ring), 1650 (CONH), 1450 (C=N).

Chromato-mass spectra, *m/z* (I_{rel}, %): 440 $[M+H]^+$ (73).

Found, %: C 68.61; H 4.11; N 9.69; S 7.57. $C_{25}H_{17}N_3O_3S$.

Calculated, %: C 68.32; H 3.90; N 9.56; S 7.29.

N-(3-(5-Amino-9,10-dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3*H*)-ylidene)benzamide (2 d).

Yield 69 %, Mp. 232 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 1.97 (3H, s, CH_3); 6.92 (1H, s, CH=); 7.15–7.26 (5H, m, H Ar); 7.34–7.46 (2H, м, H Ph); 7.68 (3H, м, H Ph, NH_2); 7.88 (1H, m, H Ar); 8.13–8.16 (1H, m, H Ar); 8.53 (1H, d, *J* = 8.4, H Ar).

^{13}C NMR, δ, ppm: 13.8 (CH_3CH=); 106.8 (CH=); 111.9, 115.4, 120.1, 122.2, 123.7(C Ar); 128.1, 129.2, 129.3, 129.4, 132.4 (C Ph); 132.9, 133.4, 135.0, 135.3, 135.7 (C Ar); 136.1 (C Ph); 138.2 (C-N); 139.3 (CH_3CH=); 151.8 (C-NH_2); 168.2 (C=N); 174.5 (COPh); 183.6 (CO); 184.4 (CO).

Chromato-mass spectra, *m/z* (I_{rel}, %): 440 $[M+H]^+$ (82).

N-(3-(4-Benzamido-9,10-dioxo-9,10-dihydro-anthracen-1-yl)-4-methylthiazol-2(3*H*)-ylidene)-benzamide (2 e).

Yield 48 %, Mp. 198 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 2.04 (3H, s, CH_3); 6.95 (1H, s, CH=); 7.36 (1H, m, H Ar); 7.72–8.27 (13H, m, H Ar); 8.88 (2H, m, H Ar); 9.36 (2H, m, H Ar); 13.30 (1H, s, NH).

^{13}C NMR, δ, ppm: 14.1 (CH_3CH=); 106.3 (CH=); 125.1, 126.5 (C Ar); 128.0, 128.1 (C Ph); 118.2 (C Ar); 128.8, 128.9, 129.4, 129.3 (C Ph); 136.2 (C Ar); 127.3, 127.2, 132.4, 133.3 (C Ph); 130.3 (C Ar); 132.5 (C Ph); 134.3, 133.7 (C Ar); 138.2 (C-N); 133.4, 133.0 (C Ar); 136.0 (C Ph); 129.5 (C Ar); 133.2 (C-NH); 138.8 (CH_3CH=); 165.7 (CO); 167.8 (C=N); 174.4 (COPh); 182.6 (CO); 184.5 (CO).

IR spectra, ν, cm^{-1}: 3345 (NHCO), 1683, 1625, 1661 (C=O quinone ring), 1650 (CONH), 1450 (C=N).

Found, %: C 70.61; H 3.81; N 7.69; S 7.77. $C_{32}H_{21}N_3O_4S$.

Calculated, %: C 70.70; H 3.89; N 7.73; S 5.90.

R^1,R^2,R^3-[(5-Phenyl-4*H*-1,2,4-triazol-3-yl)amino]-anthracene-9,10-diones 3 a–e (general method). To a stirred suspension of 0.0518 mmol of N-benzoylthiourea **1 a–e** in 30 ml of chloroform, 0.013 g (0.259 mmol) of hydrazine hydrate was added. The reaction mixture was heated under reflux for 5 h and cooled to room temperature. The precipitate formed was filtered, washed with water, and dried.

1-[(5-Phenyl-4*H*-1,2,4-triazol-3-yl)amino]-anthracene-9,10-dione (3 a).

Yield 81 %, Mp. 248 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 7.52–7.67 (5H, m, H Ar); 7.85–8.21 (7H, m, H Ar); 8.88 (1H, d, *J* = 8.7, H Ar); 12.15 (1H, s, NH); 14.16 (1H, s, NH).

IR spectra, ν, cm^{-1}: 3286 (NH triazole ring), 1683, 1622 (C=O quinone ring).

Chromato-mass spectra, *m/z* (I_{rel}, %): 367 $[M+H]^+$ (100).

Found, %: C 72.17; H 4.01; N 15.37. $C_{22}H_{14}N_4O_2$.

Calculated, %: C 72.12; H 3.85; N 15.29.

2-Methyl-1-[(5-phenyl-4*H*-1,2,4-triazol-3-yl)-amino]anthracene-9,10-dione (3 b).

Yield 78 %, Mp. 226 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 2.19 (3H, s, CH_3); 7.55–7.79 (2H, m, CH_{Ar}); 7.83–7.86 (2H, m, CH_{Ar}); 7.95–7.98 (3H, m, CH_{Ar}); 8.19–8.21 (2H, m, CH_{Ar}); 8.91 (1H, d, *J* = 7.48, H Ar); 12.69 (1H, s, NH); 14.61 (1H, s, NH).

IR spectra, ν, cm^{-1}: 3290 (NH triazole ring), 1685, 1625 (C=O quinone ring).

Found, %: C 72.69; H 4.14; N 14.68. $C_{23}H_{16}N_4O_2$.

Calculated, %: C 72.62; H 4.24; N 14.73.

1-Amino-4-[(5-phenyl-4*H*-1,2,4-triazol-3-yl)-amino]anthracene-9,10-dione (3 c).

Yield 74 %, Mp. 273 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 7.12–7.28 (4H, m, CH_{Ar}, NH_2); 7.58–7.92 (8H, m, CH_{Ar}); 8.40 (1H, d, *J* = 7.48 Hz, CH_{Ar}); 10.43 (1H, s, NH); 14.43 (1H, s, NH).

IR spectra, ν, cm^{-1}: 3361, 3315 (NH_2), 3304 (NH triazole ring), 1679, 1620 (C=O quinone ring).

Found, %: C 69.11; H 3.84; N 18.27. $C_{22}H_{15}N_5O_2$.

Calculated, %: C 69.28; H 3.96; N 18.36.

1-Amino-5-[(5-phenyl-4*H*-1,2,4-triazol-3-yl)-amino]anthracene-9,10-dione (3 d).

Yield 60 %, Mp. 260 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 7.08 (2H, m, NH_2); 7.36–7.56 (5H, m, CH_{Ar}); 7.81–8.19 (5H, m, CH_{Ar}); 8.89 (1H, d, *J* = 8.0 Hz, CH_{Ar}); 11.07 (1H, s, NH); 13.36 (1H, s, NH).

IR spectra, ν, cm^{-1}: 3359, 3312 (NH_2), 3310 (NH triazole ring), 1684, 1625 (C=O quinone ring).

Found, %: C 69.19; H 3.90; N 18.29. $C_{22}H_{15}N_5O_2$.

Calculated, %: C 69.28; H 3.96; N 18.36.

N-(9,10-Dioxo-4-[(5-phenyl-4*H*-1,2,4-triazol-3-yl)-amino]-9,10-dihydroanthracen-1-yl)benzamide (3 e).

Yield 70 %, Mp. 234 °C.

^{1}H NMR, δ, ppm (*J*, Hz): 7.39–7.69 (5H, m, CH_{Ar}); 7.87–7.97 (9H, m, CH_{Ar}); 8.71 (1H, d, *J* = 8.9 Hz, CH_{Ar}); 12.37 (1H, s, NH); 13.03 (1H, s, NH); 14.03 (1H, s, NH).

IR spectra, ν, cm^{-1}: 3328 (NH triazole ring), 1681, 1623 (C=O quinone ring), 1648 (CONH).

Found, %: C 71.61; H 4.05; N 14.31. $C_{29}H_{19}N_5O_3$.

Calculated, %: C 71.74; H 3.94; N 14.43.

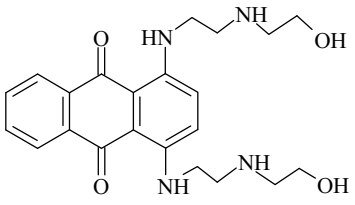
Results and discussion

Computer prediction of biological activity spectra using the PASS software

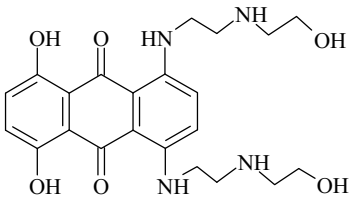
The prediction of the biological activity spectra of the synthesized compounds was performed employing the PASS computer program (Prediction of Activity Spectra for Substances) [41, 42]. The latest PASS version (2012.11.22) predicts 6400 kinds of biological activity based on the analysis of the training set including information about ~330000 drugs, drug-candidates, lead compounds, etc. The average prediction accuracy estimated in a leave-one-out cross-validation procedure for the whole training set is about 95 %. The PASS online version is freely available for a scientific community on the website [43]. Based on the PASS predictions, new pharmaceutical agents from diverse chemical classes with various kinds of biological activity have been discovered [43–45]. The PASS output is presented by a list of probable activities with two estimated probabilities: *Pa* – the probability to be "active", and *Pi* – the probability to be "inactive".

The higher the *Pa* value, the lower is the predicted probability of obtaining false positives in biological testing. For example, if one selects for testing only compounds for which a particular activity is predicted with *Pa* > 0.9, the expected probability to find inactive compounds in the selected set is very low; however, about 90 % of active compounds are missed. If one lowers the *Pa* threshold to 0.8, the probability to find inactive compounds is still low, but (only) about 80 % of active compounds are missed, etc. PASS uses the criteria *Pa* = *Pi* as the default threshold, i. e. all compounds with *Pa* >*Pi* are declared as being active.

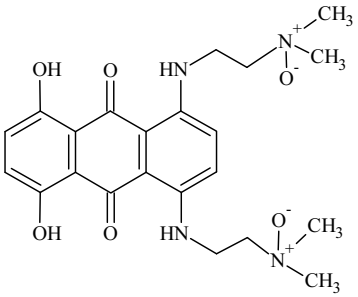
The computer prediction using the PASS Online program for such well-known anticancer drugs based on aminoderivatives of 9,10-anthraquinone as Ametantron, Mitoxantrone, Banoxantron, and compounds on preclinical studies NSC-639365 and M-18 [46] was carried out. Results are in a complete agreement with the experimental data on anticancer activity (Table 1).



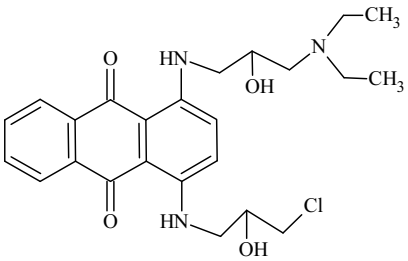
Ametantron



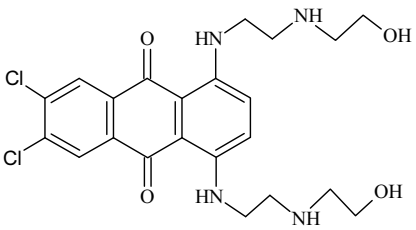
Mitoxantrone



Banoxantron



NSC-639365



M-18

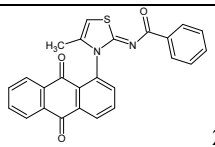
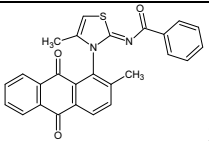
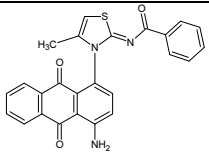
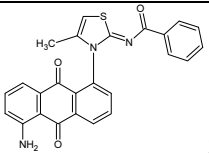
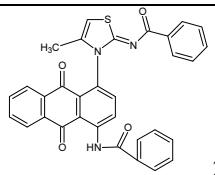
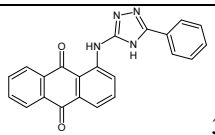
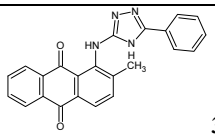
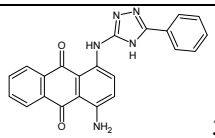
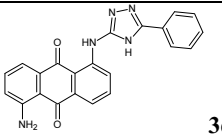
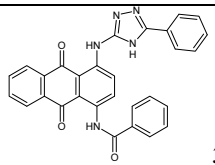
An example of the predicted pharmacological effects for Ametantron is given below (only data with *Pa* > 0.5 are shown).

Pa	*Pi*	Pharmacological effects
0.742	0.004	Radiosensitizer
0.745	0.019	Antineoplastic
0.728	0.003	Peroxidase substrate
0.715	0.006	DNA-(apurinic or apyrimidinic site) lyase inhibitor
0.701	0.005	Choline-phosphate cytidylyltransferase inhibitor
0.697	0.011	3-Hydroxybenzoate 6-monooxygenase inhibitor
0.662	0.006	Antineoplastic (non-Hodgkin's lymphoma)
0.708	0.072	Phobic disorders treatment
0.635	0.005	Alkylator
0.640	0.019	Manganese peroxidase inhibitor
0.663	0.064	CDP-glycerol glycerophosphotransferase inhibitor
0.607	0.011	CYP2E substrate
0.586	0.002	Beta-Lysine 5,6-aminomutase inhibitor
0.584	0.008	Chemosensitizer
0.657	0.083	Gluconate 2-dehydrogenase (acceptor) inhibitor
0.643	0.090	Ubiquinol-cytochrome-c reductase inhibitor
0.569	0.023	Fibrolase inhibitor
0.560	0.017	Cytostatic
0.602	0.062	CYP2J2 substrate
0.578	0.039	Glucose oxidase inhibitor
0.613	0.082	CYP2J substrate
0.532	0.003	Acetylenecarboxylate hydratase inhibitor
0.597	0.074	CYP2C12 substrate
0.560	0.036	General pump inhibitor
0.527	0.008	Antineoplastic (multiple myeloma)
0.521	0.005	DNA intercalator
0.522	0.006	RNA synthesis inhibitor
0.546	0.031	Hydrogen dehydrogenase inhibitor
0.545	0.030	Superoxide dismutase inhibitor
0.555	0.041	Aldehyde oxidase inhibitor
0.556	0.044	Macrophage colony stimulating factor agonist
0.500	0.003	Antineoplastic, alkylator

Table 1. Predicted antineoplastic (anticancer) activity using the PASS program for known derivatives of 9,10-anthraquinone with anticancer activity

Compound / Activity Pa	Antineoplastic	Antineoplastic (non-Hodgkin's lymphoma)	Antineoplastic (multiple myeloma)
Ametantron	0.745	0.662	0.527
Mitoxantrone	0.798	0.671	0.536
Banoxantron	0.906	0.868	0.366
NSC-639365	0.737	0.547	0.859
M-18	0.646	0.641	0.521

Table 2. Typical activities predicted for new 2-iminothiazole **2 a–e** and 1,2,4-triazole **3 a–e** derivatives of 9,10-anthraquinone (*Pa* >0.4)

Compound / Activity (Pa)	Mucomembranous protector	Transcription factor STAT3 inhibitor	Antineoplastic (non-Hodgkin's lymphoma)	Muramoyltetrapeptide carboxypeptidase inhibitor	Antineoplastic	Angiogenesis inhibitor	3-Hydroxybenzoate 6-monooxygenase inhibitor	Protein kinase inhibitor	Pterin deaminase inhibitor	Antiarthritic
 **2a**	0.684	0.508	-	0.596	-	-	-	-	-	-
 **2b**	0.648	0.500	-	0.566	-	-	-	-	-	-
 **2c**	0.421	-	0.430	0.527	-	-	-	-	-	-
 **2d**	0.421	-	0.430	0.527	-	-	-	-	-	-
 **2e**	0.451	0.499	-	0.486	-	-	-	-	-	-
 **3a**	0.684	-	0.436	-	0.810	0.885	0.834	0.443	0.589	0.500
 **3b**	0.648	-	0.411	-	0.774	0.813	0.684	0.557	0.545	0.441
 **3c**	0.421	-	0.491	-	0.811	0.846	0.708	0.434	0.553	0.432
 **3d**	-	-	0.491	-	0.811	0.846	0.708	0.434	0.553	0.432
 **3e**	-	-	0.456	-	0.781	0.864	0.646	0.401	-	0.558

Note: "-" predictive activity is absent when *Pa* > 0.4.

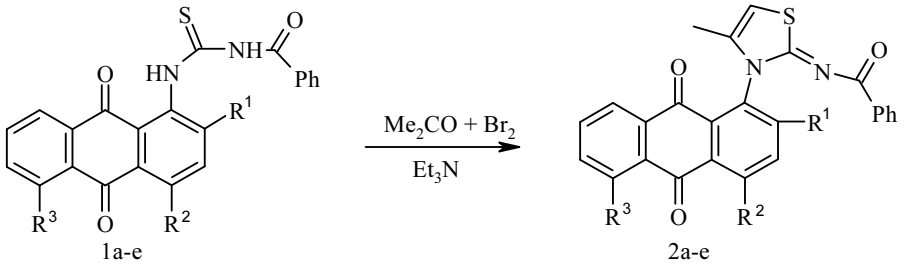
The data obtained in experimental biological testing and calculated using the computer on-line PASS program provided the basis for predicting probable spectrum of anticancer activity of a series of new azole derivatives of 9,10-anthraquinone (Table 2).

Some predicted typical pharmacological effects for ten new compounds – 2-iminothiazoles **2 a–e** and 1,2,4-triazoles **3 a–e** – are shown in Table 2 (*Pa* > 0.4), which include: *mucomembranous protector, transcription factor STAT3 inhibitor, antineoplastic, muramoyl-tetrapeptide carboxypeptidase inhibitor, angiogenesis inhibitor, 3-hydroxybenzoate 6-monooxygenase inhibitor, protein kinase inhibitor, pterin deaminase inhibitor, antiarthritic,* etc. In the view of these data calculated using the PASS, the synthesis of new biheterocyclic structures, including 9,10-anthraquinone, and thiazole or triazole fragments seems reasonable.

Chemistry

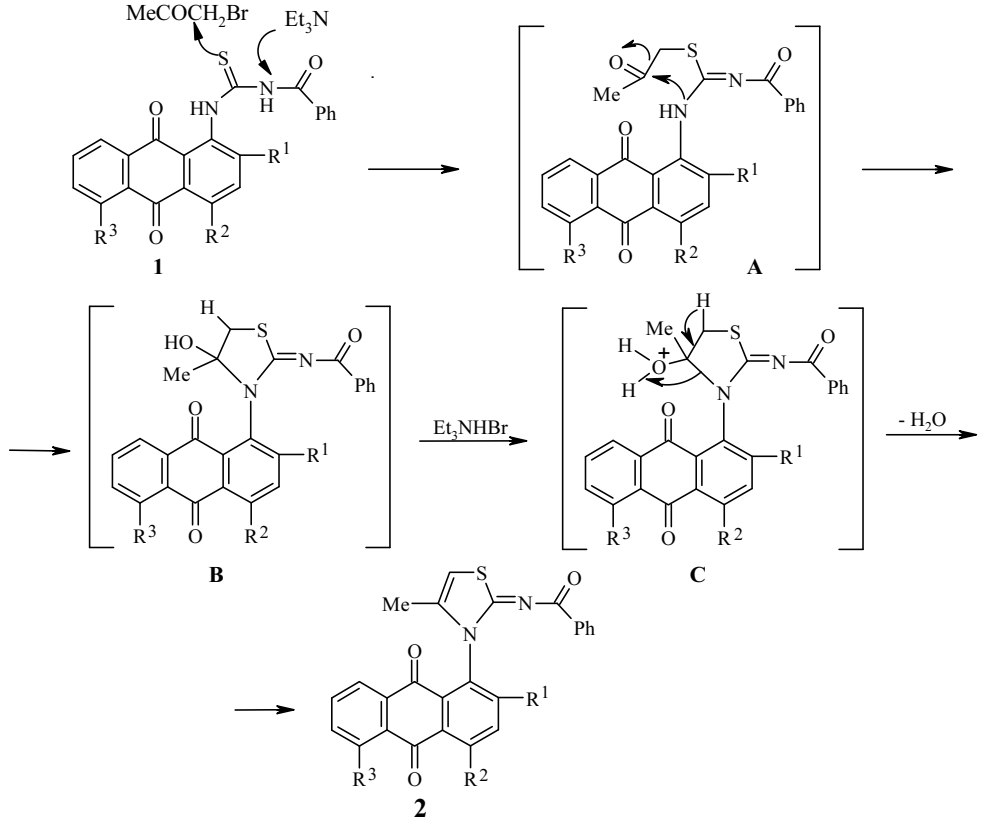
Benzoylthioureas **1 a–e** synthesized as described previously [47] were used to obtain new potentially antineoplastic derivatives of 9,10-anthraquinone. Their reaction with prepared *in situ* α-bromoacetone in acetone in the presence of triethylamine gave N-[3-(R^1,R^2,R^3)-9,10-dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3H)-ylidene]benzamides **2 a–e** in 48–68 % yields (Scheme 1).

According to literature data [5, 13], a probable formation of the 2-iminothiazole cycle of compounds **2 a–e** is presented in Scheme 2 and involves the initial attack of triethylamine on a more acidic imide proton of thiourea fragment **1** and the subsequent attack of a sulfur atom of thiourea on a carbon atom of the bromomethyl group of bromoacetone providing the isothiourea intermediate **A**. The intramolecular attack of the secondary NH-group on the carbon atom of the carbonyl group leads to the formation of the cyclic intermediate **B** which, through the intermediate stage of the oxonium intermediate **C** dehydration, gives the target product **2**.



R^1=R^2=R^3=H (a); R^1=Me, R^2=R^3=H (b); R^1=R^3=H, R^2=NH_2 (c);
R^1=R^2=H, R^3=NH_2 (d); R^1=R^3=H, R^2=NHCOPh (e)

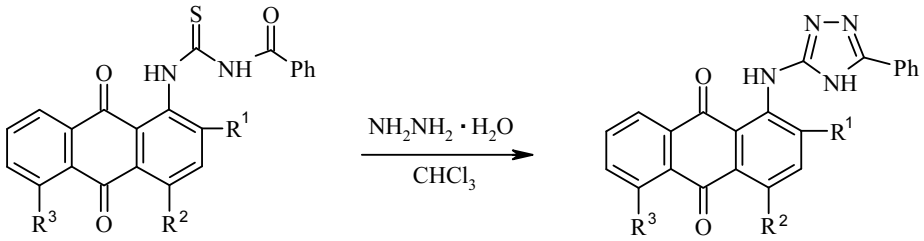
Scheme 1. Synthesis of N-[3-(R^1,R^2,R^3)-9,10-dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3H)-ylidene]benzamides **2 a–e**



Scheme 2. Mechanism of the formation of N-[3-(R^1,R^2,R^3)-9,10-dioxo-9,10-dihydroanthracen-1-yl)-4-methylthiazol-2(3H)-ylidene]benzamides **2 a–e**

In the ^{1}H NMR spectra of compounds **2 a–e**, along with the signals of aromatic protons, singlets of H-5 protons of the thiazole cycle (6.89–7.01 ppm) and methyl groups (1.97–2.04 ppm) are present. The formation of thiazole cycle was reliably confirmed by the ^{13}C NMR spectra displaying the characteristic singlets of C^4, C^5 and C^2 atoms at 106.1–107.2, 139.3–144.9, and 168.2–169.7 ppm, respectively.

The synthesis of novel 1,2,4-triazole derivatives of 9,10-anthraquinone was carried out by the procedure described in [6]. Benzoylthioureas **1 a–e** were heated with hydrazine hydrate in a ratio of 1 : 5 in refluxing chloroform. As a result, triazolylaminoanthracenes **3 a–e** were obtained with 60–81 % yields (Scheme 3).



1a-e 3a-e

R^1=R^2=R^3=H (a); R^1=Me, R^2=R^3=H (b); R^1=R^3=H, R^2=NH_2 (c); R^1=R^2=H, R^3=NH_2 (d); R^1=R^3=H, R^2=NHCOPh (e)

Scheme 3. Synthesis of R^1,R^2,R^3-[(5-phenyl-4*H*-1,2,4-triazol-3-yl)amino]anthracen-9,10-diones **3 a–e**

In the IR spectra of the synthesized compounds, characteristic absorption bands of two carbonyl groups of an anthraquinone fragment within the 1620–1685 cm^{-1} and the ones for the NH group of the triazole cycle at 3304–3328 cm^{-1} are present. In the ^{1}H NMR spectra of the triazole derivatives **3 a–e**, the singlets of the aminotriazole cycle proton are present at 14.03–14.63 ppm.

Conclusions

New potentially biologically active N-(9,10-dioxo-9,10-dihydroanthracene-1-yl)-2-(N-benzoyilimino)thiazoles and [(5-phenyl-4H-1,2,4-triazol-3-yl)amino]anthracene-9,10-diones were obtained by the reaction of N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracene-1-yl)thioureas with bromoacetone and hydrazine hydrate, respectively. The mechanism of N-[3-(R^1,R^2,R^3)-9,10-dioxo-9,10-dihydro-anthracen-1-yl)-4-methylthiazol-2(3H)-ylidene]benzamides formation was proposed. The biological activity spectra of the synthesized compounds have been estimated by using the PASS computer program.

Acknowledgements

This work was performed with a partial financial support of the State Fund for Fundamental Research of Ukraine (agreement # F53/97-2013) and the Russian Foundation for Basic Research (grant # 13-04-90425).

References

1. **Hartung J., Rosenbaum K., Beyer L., Fernandes V.** Zur reversiblen umwandlung von 3-diethylamino-5-phenyl-1,2,4-dithiazolium-halometallaten in metallchelate der 3-(thio)benzoyl(thio)harnstoffe // J. Prakt. Chem. 1991. Vol. 333. P. 537–544. http://dx.doi.org/10.1002/prac.19913330404
2. **Zeng R.-S., Zou J.-P., Zhi S.-J., Chen J., Shen Q.** Aldol- and Mannich-type reactions via *in situ* olefin migration in ionic liquid // Org. Lett. 2003. Vol. 5. P. 657–660. http://dx.doi.org/10.1021/ol0273102
3. **Manaka A., Ishii T., Takahashi K.** 2-Acylimino-3-alkyl-3H-thiazoline derivatives: one-pot, three-component condensation synthesis of novel β-turn mimics // Tetrahedron Lett. 2005. Vol. 46. N 3. P. 419–422. http://dx.doi.org/10.1016/j.tetlet.2004.11.105.
4. **Wang X., Wang F., Quan Z., Zhang Z., Wang M.** One-pot synthesis of 2-acylimino-3-arylthiazoline derivatives in aqueous media // Synt. Commun. 2006. Vol. 36. P. 2453–2460. http://dx.doi.org/10.1080/00397910600781208
5. **Murru S., Singh C. B., Kalava V., Patel B. K.** A convenient one-pot synthesis of thiazol-2-imines: application in the construction of pifithrin analogues // Tetrahedron. 2008. Vol. 64. P. 1931–1942. http://dx.doi.org/10.1016/j.tet.2007.11.076
6. **Kodomari M., Suzuki M., Tanigawa K., Aoyoma T.** A convenient and efficient method for the synthesis of mono- and N,N-disubstituted thioureas // Tetrahedron Lett. 2005. Vol. 46. P. 5841–5843. http://dx.doi.org/10.1016/j.tetlet.2005.06.135
7. **Aly A. A., Ahmed E. K., El-Mokadam K. M.** Reactions of aroylthioureas with acetylenic esters and dibenzoyl ethylene. Selectivity towards the formation of new 1,3-thiazines // J. Heterocycl. Chem. 2007. Vol. 44. P. 1431–1438. http://dx.doi.org/10.1002/jhet.5570440630
8. **Aly A. A., Brown A. B., Ramadan M., Abdel-Aziz M., Abuo-Rahma G., Radwan M. F., Gamal-Eldeen A. M.** Selectivity of N-aroyl-N′-arylthioureas towards 2-(1,3-dioxo-1H-inden-2(3H)-ylidene)malononitrile. New synthesis of (Z)-N-((E)-4-amino-1-aryl-5-cyano-6-oxo-1H-indeno[1,2-d][1,3]-thiazepin-2(6H)-ylidene)-4-arylamides of antitumor and antioxidant activities // J. Heterocycl. Chem. 2010. Vol. 47. N 3. P. 503–508. http://dx.doi.org/10.1002/jhet.344

9. **Huang D, Ding Y, Luo W. M, Bender S, Qian C. N, Kort E, Zhang Z. F, VandenBeldt K, Duesbery N. S, Resau J. H, Teh B. T.** Inhibition of MAPK kinase signaling pathways suppressed renal cell carcinoma growth and angiogenesis *in vivo* // Cancer Res. 2008. Vol. 68. P. 81–88. http://dx.doi.org/10.1158/0008-5472.CAN-07-5311.
10. **Tomizawa M., Kagabu S., Ohno I., Durkin K. A., Casida J. E.** Potency and selectivity of trifluoroacetylimino and pyrazinoylimino nicotinic insecticides and their fit at a unique binding site niche // J. Med. Chem. 2008. Vol. 51. P. 4213–4218. http://dx.doi.org/10.1021/jm800191a
11. **Zhang N., Tomizawa M., Casida J. E.** Structural features of azidopyridinyl neonicotinoid probes conferring high affinity and selectivity for mammalian α4β2 and drosophila nicotinic receptors // J. Med. Chem. 2002. Vol. 45. P. 2832–2840. http://dx.doi.org/10.1021/jm010508s
12. **Walczynski K., Guryn R., Zuiderveld O. P., Zhang M.-Q., Timmerman H.** Histamine H1 receptor ligands: Part II. Synthesis and *in vitro* pharmacology of 2-[2-(phenylamino)thiazol-4-yl]ethanamine and 2-(2-benzhydrylthiazol-4-yl)ethanamine derivatives // Farmaco. 2000. Vol. 55. P. 569–574. http://dx.doi.org/10.1016/S0014-827X(00)00087-2
13. **Singh C. B., Murru S., Kavala V., Patel B. K.** It is "thiazolidene-2-imine" and not imidazole-2-thione as the reaction product of 1-benzoyl-3-phenylthiourea with Br_2/enolizable ketone // Org. Lett. 2006. Vol. 8. N 23. P. 5397–5399. http://dx.doi.org/10.1021/ol062371b
14. **Singh C. B., Murru S., Kavala V., Patel B. K.** 3-Aryl-1-benzoylthioureas with α-bromoketones in water form 2-N-benzoyl-3-arylthiazol-2(3H)-imines, not 3-aryl-1-benzoylimidazoline-2-thiones // J. Chem. Res. 2007. Vol. 3. P. 136–137. http://dx.doi.org/10.3184/030823407X196719
15. **De Kimpe N., Boelens M., Declereq J.-P.** A Novel synthesis of 2-imino-4-thiazolines via α-bromoketimines // Tetrahedron. 1993. Vol. 49. N 16. P. 3411–3424. http://dx.doi.org/10.1016/S0040-4020(01)90168-1.
16. **D'hooghe M., Waterinckx A., De Kimpe N.** A novel entry toward 2-imino-1,3-thiazolidines and 2-imino-1,3-thiazolines by ring transformation of 2-(thiocyanomethyl)aziridines // J. Org. Chem. 2005. Vol. 70. P. 227–232. http://dx.doi.org/10.1021/jo048486f
17. **Kasmi S., Hamelin J., Benhaoua H.** Microwave-assisted solvent-free synthesis of iminothiazolines // Tetrahedron Lett. 1998. Vol. 39. P. 8093–8096. http://dx.doi.org/10.1016/S0040-4039(98)01836-X
18. **Zhu X. X., Yu Q. S., Culter R. G., Culmsee C. W., Holloway H. W., Lahiri D. K., Mattson M. P., Greig N. H.** Novel p53 inactivators with neuroprotective action: Syntheses and pharmacological evaluation of 2-imino-2,3,4,5,6,7-hexahydrobenzothiazole and 2-imino-2,3,4,5,6,7-hexahydrobenzoxazole derivatives // J. Med. Chem. 2002. Vol. 45. P. 5090–5097. http://dx.doi.org/10.1021/jm020044d
19. **Ivanov Y. Y., Tkachenko S. E., Proshin A. N., Bachurin S. O.** Derivatives of 2-amino-2-thiazoline – novel chemotype with muscarinomimetic activity // Biomed. Khim. 2003. Vol. 49. N 1. P. 92–95.
20. **Baumann R. J., Mayer G. D., Fite L. D., Gill L. M., Harrison B. L.** *In vitro* and *in vivo* candicidal activities of 2-(p-n-hexylphenylamino)-1,3-thiazoline // Chemotherapy 1991. Vol. 37. P. 157–165. http://dx.doi.org/10.1159/000238849
21. **Sondhi S. M., Singh N., Lahoti A. M., Bajaj K., Kumar A., Lozach O., Meijer L.** Synthesis of acridinyl-thiazolino derivatives and their evaluation for anti-inflammatory, analgesic and kinase inhibition activities // Bioorg. Med. Chem. 2005. Vol. 13. P. 4291–4299. http://dx.doi.org/10.1016/j.bmc.2005.04.017
22. **Matsuda H., Shimoda H., Yoshikawa M.** Dimeric sesquiterpene thioalkaloids with potent immunosuppressive activity from the rhizome of *Nuphar pumilum*: structural requirements of *Nuphar* alkaloids for immunosuppressive activity // Bioorg. & Med. Chem. 2001. Vol. 9. N 4. P. 1031–1035. http://dx.doi.org/10.1016/S0968-0896(00)00327-8
23. **Webel L. M., Degnam M. B., Harger G. F., Capps D. B., Islip P. J., Closier M. D.** Terpene compounds as drugs. 11. Anabolic 19-nortestosterone terpenoates // J. Med. Chem. 1972. Vol. 15. P. 995–998. http://dx.doi.org/10.1021/jm00279a031
24. **Nagasaki F., Yamada T., Takahashi E., Kitagawa Y., Hatano R.** Jpn. Kokai Tokkyo Koho JP 63250371, 1988.
25. **Hoelzel H., Creuzburg D., Stohr P., Dehne H., Teller J., Kranz L., Luthardt H., Roethling T., Kaestner A.** Ger. DD 258168, 1988.
26. **Bae S., Hahn H. G., Nam K. D., Mah H.** Solid-phase synthesis of fungitoxic 2-imino-1,3-thiazolines // J. Comb. Chem. 2005. Vol. 7. P. 7–9. http://dx.doi.org/10.1021/cc049854w
27. **Kim D.-S., Joeng Y.-M., Park I.-K., Hahn H.-G., Lee H.-K., Kwon S.-B., Jeong J. H., Yang S. J. Sohn U. D., Park K.-C.** A new 2-imino-1,3-thiazoline derivative, KHG22394, inhibits melanin synthesis in mouse B16 melanoma cells // Biol. Pharm. Bull. 2007. Vol. 30. P. 180–183. http://dx.doi.org/10.1248/bpb.30.180
28. **Tsukuda T., Shiratori Y., Watanabe M., Ontsuka H., Hattori K., Shirai M., Shimma N.** Modeling, synthesis and biological activity of novel antifungal agents (1) // Bioorg. Med. Chem. Lett. 1998. Vol. 8. P. 1819–1824. http://dx.doi.org/10.1016/S0960-894X(98)00316-3
29. **Witkoaski J. T., Robins R. K., Sidwell R. W., Simon L. N.** Design, synthesis, and broad spectrum antiviral activity of 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide and related nucleosides // J. Med. Chem. 1972. Vol. 15. P. 1150–1154. http://dx.doi.org/10.1021/jm00281a014
30. **Heubach G., Sachse B., Buerstell H.** Ger. Offen. 826760, 1979.
31. **Tanaka G.** Japan Kokai. 973. 7495. 1974
32. **Griffin D. A., Mannion S. K**. Eur. Pat. Appl. EP 199,474, 1986.
33. **Hanna N. B., Dimitrijevich S. D., Larson S. B., Robsin R. K., Revankar G. R.** Synthesis and single-crystal X-ray diffraction studies of 1-β-D-ribofuranosyl-1,2,4-triazole-3-sulfonamide and certain related nucleosides // J. Heterocycl. Chem. 1988. Vol. 25. P. 1857–1868. http://dx.doi.org/10.1002/jhet.5570250649
34. **Jenkins T. C., Stratford I. J., Stephens M. A.** 3-Nitro-1,2,4-triazoles as hypoxia-selective agents // Anticancer Drug Des. 1989. Vol. 4. P. 145–160.
35. **Husain M. I., Amir M.** Synthesis of some new substituted thiosemicarbazides and triazoles as possible anticonvulsants // J. Indian Chem. Soc. 1986, Vol. 63. P. 317–319.

36. **Chiu S.-H. L., Huskey S.-E. W.** Species differences in *N*-glucuronidation // Drug Metabol. Dispos. 1998. Vol. 26. P. 838–847.
37. **Eliott R., Sunley R. L., Griffin D. A.** PrepUK PatAppl GB 2 175 301, 1986.
38. **Lown J. W.** Anthracycline and anthracendione-based anticancer agents. Elsevier Science Publ. B. V. Amsterdam–Oxford–New York–Tokyo. 1988. 738 p.
39. **Delmulle L., Demeyer K.** Anthraquinones in plants: source, safety and applications in gastrointestinal health. Nottingham University Press. 2010. 157 p.
40. **Файн В. Я.** 9,10-Антрахиноны и их применение. Центр фотохимии РАН. Москва. 1999. 92 с.
41. **Poroikov V. V., Filimonov D. A.** How to acquire new biological activities in old compounds by computer prediction // J. Comput. Aid. Molec. Des. 2002. Vol. 11. P. 819–824. http://dx.doi.org/10.1023/A:1023836829456
42. **Filimonov D. A., Poroikov V. V.** In: Chemoinformatics Approaches to Virtual Screening. Eds. Alexandre Varnek and Alexander Tropsha. Cambridge, RSC Publishing, 2008. P. 182–216. http://dx.doi.org/10.1039/9781847558879-00182
43. URL [http://www.way2drug.com/passonline]
44. **Geronikaki A., Druzhilovsky D., Zakharov A., Poroikov V.** Computer-aided predictions for medicinal chemistry via Internet // SAR and QSAR in Environ. Res. 2008. Vol. 19. P. 27–38. http://dx.doi.org/10.1080/10629360701843649
45. **Kryzhanovskii S. A., Salimov R. M., Lagunin A. A., Filimonov D. A., Gloriozova T. A., Poroikov V. V.** Nootropic action of some antihypertensive drugs: computer predicting and experimental testing // Pharmaceut. Chem. J. 2012. Vol. 45. 10. P. 605–611.
46. URL: [http://integrity.thomson-pharma.com]
47. **Stasevych M., Zvarych V., Musyanovych R., Novikov V., Vovk M.** Synthesis of N-benzoyl-N'-(9,10-dioxo-9,10-dihydroanthracene-1-yl)-thioureas and quantum-chemical analysis of the reaction passing // Chemistry & Chemical Technology. 2014. Vol. 3 (in press).

V. Zvarych, M. Stasevych, O. Stanko, V. Novikov, M. Vovk, V. Poroikov, O. Solovyov

NAUJŲ N-BENZOIL-N'-(9,10-DIOKSO-9,10-DIHIDROANTRACEN-1-IL)TIOŠLAPALO PAGRINDU AZOLO DARINIŲ SINTEZĖ IR KOMPIUTERINIS JŲ AKTYVUMO VERTINIMAS

S a n t r a u k a

Nauji 9,10-antrachinono dariniai, turintys tiazolo arba 1,2,4-triazolo fragmentus, buvo susintetinti reaguojant N-benzoil-N'-(9,10-diokso-9,10-dihidroantracen-1-il)tiošlapalo dariniams su bromacetonu, reakcijos terpėje esant trietilaminui arba hidrazino hidratui chloroforme. Panaudojant PASS kompiuterinę programą, buvo apskaičiuoti biologinio aktyvumo spektrai, siekiant atrinkti kiek įmanoma aktyviausius junginius biologinio aktyvumo tyrimams atlikti. Šie skaičiavimai parodė, kad susintetinti junginiai turėtų būti labai biologiškai aktyvūs.