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THE NEW 1,2,3-TRIAZOLYLANTRACENE-9,10-DIONES: SYNTHESIS AND COMPUTER BIOACTIVITY SCREENING

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Abstract. The reactions of 1,4(1,5)-diazido-9,10-anthracenediones with phenylacetylene and methyl propiolate under copper(I)-catalyzed reaction of the azide-alkyne cycloaddition conditions have been studied and a series of new 1,2,3-triazole derivatives of 9,10-anthracendione have been obtained. The computer screening of synthesized compounds was carried out using the *PASS Online* software to identify areas of experimental biomedical researches. Compounds with high affinity to the receptors family of tyrosine kinases of the epidermal growth factor EGFR have been found among the newly synthesized 1,2,3-triazoles of 9,10-anthracenedione using molecular docking. The results of molecular docking indicate a probable mechanism for the realization of antitumor activity.

Keywords: 1(2)-azido-9,10-anthracenediones, 1,4(1,5)-diazido-9,10-anthracenediones, acetylenes, 1,3-dipolar cycloaddition, 1,2,3-triazoles, computer screening.

1. Introduction

1,2,3-Triazoles are an important class of heterocyclic compounds, which are of theoretical and practical interest in synthetic organic chemistry, as well as possess a wide range of pharmacological properties. The compounds with antimicrobial, antiviral, anti-proliferating, anti-HIV, anti-hepatitis, insecticidal, fungicidal, growth regulative, anti-inflammatory, and antitumor activity which have been identified among the derivatives of 1,2,3-triazole [1, 2]. 1,2,3-Triazole compounds are attractive biochemical and medical objects because they can easily bind with biological targets through hydrogen bonding and dipole interactions [3, 4].

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The 1,3-dipolar reaction of azide-alkyne cycloaddition is one of effective methods for the synthesis of 1*H*-1,2,3-triazoles [1]. The classic version of this reaction proceeds through the mechanism of 1,3-dipolar addition and formation of mixture of isomeric 1,4- and 1,5-disubstituted 1,2,3-triazoles. The reaction of 1,3-dipolar cycloaddition was widely developed after invention of copper-catalyzed version by N. Meldal [5] and B. Sharpless [6] in the year 2002. It is the main reaction within the concept of "click chemistry" [7].

Since 1,2,3-triazole systems based on the 9,10-anthracenediones have not been known in the literature, the construction of new structures with 9,10-anthracenedione and 1,2,3-triazole moieties is very promising from the standpoint of expanding a series of previously investigated derivatives of 9,10-anthracenedione [8-12].

Thus, the synthesis of new derivatives of 9,10-anthracenedione with 1,2,3-triazole moiety and computer screening of biological action for determination of the directions of their experimental studies were the aim of this work.

2. Experimental

The spectra of ^{1}H and ^{13}C NMR of synthesized compounds were obtained on the device spectrometer Varian Mercury-400 (399.9601 and 125.728 MHz, respectively) in solutions DMSO-d_6, TMS internal standard. LC-MS spectra were recorded on Agilent 110\DAD\HSD\VLG 119562. IR spectra were obtained on spectrophotometer Specord M-80 in tablets of KBr. Individuality compounds was controlled by TLC on plates Silufol UV-254 in a solvent system benzene-acetonitrile 6: 1.

1-azide-9,10-anthracenedione 1 [13], **2-azide-9,10-anthracenedione 2** [14], **1,4- and 1,5-diazido-9,10-anthracenediones 13,14** [15].

General method of obtaining of (1*H*-1,2,3-triazole-1(2)-yl)anthracene-9,10-diones 3-10. To the freshly prepared azide of 9,10-anthracendione (0.5 g,

2.241 mmol/0.5 g, 2.099 mmol for diazide) in 30 ml of chloroform is added an equimolar amount of the appropriate acetylene derivative (or double amount for diazide), triethylamine (0.272 g, 2.688 mmol/0.51 g, 5.037 mmol) and copper(I) iodide (0.043 g, 0.224 mmol/0.086 g, 0.448 mmol). The reaction mixture was stirred for 10 h at room temperature. The precipitate was filtered, then it was extracted with acetonitrile, filtered, and the filtrate was evaporated.

Compounds **15-18** were isolated on chromatographic column (silica gel), eluent – benzene:acetonitrile (6:1).

1-(4-Phenyl-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 3. Yield 61 %. Mp. = 528–530 K. ^{1}H NMR spectrum, δ, ppm: 7.39–7.49 m (3H, CH_{ar}); 7.95–8.23 m (8H, CH_{ar}); 8.49–8.51 m (1H, CH_{ar}); 8.96 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 124.27 (CH=); 125.91, 127.15, 127.53, 128.37, 128.68, 129.64, 129.66, 131.23, 132.79, 134.61, 134.62, 134.66, 135.11, 135.42, 135.45 (C_{ar}), 136.1 (C-N); 149.21 (C-Ph); 181.77, 182.35 (C=O). IR spectrum, ν, cm^{-1}: 1441 (N=N), 1671, 1645 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 352 [M+H] (99). Found, %: C 75.34; H 3.79; N 11.86. $C_{22}H_{13}N_3O_2$. Calculated, %: C 75.20; H 3.73; N 11.96.

2-(4-Phenyl-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 4. Yield 68 %. Mp. = 505–507 K. ^{1}H NMR spectrum, δ, ppm: 7.34–7.54 m (3H, CH_{ar}); 7.96–8.69 m (9H, CH_{ar}); 9.65 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 122.95 (CH=); 119.94, 121.69, 126.47, 126.76, 127.24, 128.81, 128.87, 128.92, 130.10, 130.57, 132.67, 133.03, 134.37, 134.41, 134.9 (C_{ar}); 140.34 (C-N), 149.41 (C-Ph); 180.67, 182.59 (C=O). IR spectrum, ν, cm^{-1}: 1438 (N=N), 1681, 1639 (C=O quinone ring). LC-MS spectrum, *m/z* ($I_{rel,}$ %): 352 [M+H] (100). Found, %: C 75.29; H 3.69; N 11.90. $C_{22}H_{13}N_3O_2$. Calculated, %: C 75.20; H 3.73; N 11.96.

1-(4-(Hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 5. Yield 68 %. Mp. = 494––495 K. ^{1}H NMR spectrum, δ, ppm: 4.82 d (2H, J=14.4 Hz, CH_2); 5.29 t (1H, J=7 Hz, OH); 7.13–7.15 m (1H, CH_{ar}); 7.32–7.36 m (1H, CH_{ar}); 7.76–7.87 m (2H, CH_{ar}); 8.07–8.09 m (1H, CH_{ar}); 8.21–8.23 m (2H, CH_{ar}); 8.64 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 56.03 (CH_2); 121.94 (CH=) 123.47, 124.25, 126.47, 127.04, 127.21, 132.67, 133.45, 133.86, 134.10, 134.43, 134.90 (C_{ar}); 136.65 (C-N), 150.97 (CH=C); 182.27, 182.61 (C=O). IR spectrum, ν, cm^{-1}: 1445 (N=N), 1680, 1631 (C=O quinone ring), 3100 (CH_2OH). LC-MS spectrum, m/z ($I_{rel.,}$ %): 306 [M+H] (99.8). Found, %: C 66.95; H 3.72; N 13.82. $C_{17}H_{11}N_3O_3$. Calculated, %: C 66.88; H 3.63; N 13.76.

2-(4-(Hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 6. Yield 70 %. Mp. = 503––504 K. ^{1}H NMR spectrum, δ, ppm: 4.64 d (2H, J=14.4 Hz, CH_2); 5.39 m (1H, J=7 Hz, OH); 7.93–7.94 m (2H, CH_{ar}); 8.19–7.23 m (2H, CH_{ar}); 8.33–8.42 m (2H, CH_{ar}); 8.61 s (1H, CH_{ar}); 8.96 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 54.92 (CH_2); 116.77 (CH=) 121.41, 124.55, 126.91, 126.95, 129.17, 132.13, 132.93, 132.98, 133.02, 134.66, 134.91 (C_{ar}); 140.55 (C-N), 149.83 (CH=C); 181.41, 181.71 (C=O). IR spectrum, ν, cm^{-1}: 1431 (N=N), 1674, 1642 (C=O quinone ring), 3115 (CH_2OH). LC-MS spectrum, m/z (I_{rel}, %): 306 [M+H] (100). Found, %: C 66.95; H 3.72; N 13.82. $C_{17}H_{11}N_3O_3$. Calculated, %: C 66.88; H 3.63; N 13.76.

Methyl 1-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-1*H*-1,2,3-triazol-4-carboxylate 7. Yield 62 %. Mp. = = 513–515 K. ^{1}H NMR spectrum, δ, ppm: 3.93 s (3H, CH_3); 7.96–7.98 m (2H, CH_{ar}); 8.26–8.28 m (2H, C_{Har}); 8.43–8.45 m (1H, CH_{ar}); 8.56–8.57 m (1H, CH_{ar}); 8.75 m (1H, CH_{ar}); 9.86 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 52.49 (CH_3); 123.58, 124.26, 126.49, 127.22, 127.28, 127.57, 132.53, 133.76, 133.89, 134.08, 134.48, 134.86 (C_{ar}); 137.31 (C-N); 143.13 (CH=C); 160.55 (COO); 181.81, 182.61 (C=O). IR spectrum, ν, cm^{-1}: 1452 (N=N), 1669, 1648 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 334 [M+H] (99). Found, %: C 64.79; H 3.39; N 12.53. $C_{18}H_{11}N_3O_4$. Calculated, %: C 64.87; H 3.33; N 12.61.

Methyl 2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-1*H*-1,2,3-triazol-4-carboxylate 8. Yield 65 %. Mp. = =518–520 K. ^{1}H NMR spectrum, δ, ppm: 3.92 s (3H, CH_3); 7.94–8.24 m (6H, CH_{ar}); 8.51–8.53 m (1H, CH_{ar}); 9.19 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 52.51 (CH_3); 117.21 (C_{ar}); 120.71 (CH=), 125.79, 126.45, 126.76, 128.33, 130.10, 133.03, 134.35, 134.41, 134.43, 134.90 (C_{ar}); 141.81 (C-N), 142.84 (C-COOMe), 161.10 (COO); 180.67, 182.59 (C=O). IR spectrum, ν, cm^{-1}: 1462 (N=N), 1672, 1638 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 334 [M+H] (100). Found, %: C 64.81; H 3.41; N 12.57. $C_{18}H_{11}N_3O_4$. Calculated, %: C 64.87; H 3.33; N 12.61.

Ethyl 1-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-1*H*-1,2,3-triazol-4-carboxylate 9. Yield 62 %. Mp. = = 535–537 K. ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, J = = 8 Hz, CH_3); 4.50–4.56 m (2H, CH_2); 7.84–7.88 m (1H, CH_{ar}); 8.17–8.39 m (3H, CH_{ar}); 8.33–8.43 m (2H, CH_{ar}); 8.49–8.54 m (1H, CH_{ar}); 9.44 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 14.57 (CH_3); 61.32 (CH_2) 122.89, 123.96, 126.27, 126.91, 127.12, 127.62, 131.83, 133.15, 133.57, 133.94, 134.62, 134.72 (C_{ar}); 137.52 (C-N); 142.58 (CH=C); 159.96 (COO); 181.93, 182.84 (C=O). IR spectrum, ν, cm^{-1}: 1472 (N=N), 1677, 1649 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 348 [M+H] (93). Found, %: C 65.64; H 3.85; N 12.03. $C_{19}H_{13}N_3O_4$. Calculated, %: C 65.70; H 3.77; N 12.10.

Ethyl 2-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-1*H*-1,2,3-tryazol-4-carboxylate 10. Yield 65 %. Mp. = 512–513 K. ^{1}H NMR spectrum, δ, ppm: 1.34 s (3H,

J = 8 Hz, CH_3); 4.36–4.41 m (2H, CH_2); 7.86–8.09 m (4H, CH_{ar}); 8.21–8.35 m (3H, CH_{ar}); 9.14 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 14.61 (CH_3); 60.61 (CH_2) 117.05; 120.42, 123.61, 126.36, 126.85, 127.13, 127.62, 131.50, 132.43, 132.51, 132.85, 133.77, 133.98 (C_{ar}); 142.64 (C-N), 161.12 (COO); 181.87, 182.92 (C=O). IR spectrum, ν, cm^{-1}: 1469 (N=N), 1681, 1647 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 348 [M+H] (93). Found, %: C 65.78; H 3.71; N 12.17. $C_{19}H_{13}N_3O_4$. Calculated, %: C 65.70; H 3.77; N 12.10.

Dimethyl 1-(9,10-dioxo-9,10-dihydroanthracen-1-yl)-1H-1,2,3-triazol-4-carboxylate 11. To freshly prepared azide (0.5 g, 2.241 mmol) in 30 ml of chloroform was added an equimolar amount of dimethyl acetylenedicarboxylate. The reaction mixture was stirred for 12 h at room temperature; the precipitate was filtered, dried and crystallized from acetonitrile.

Yield 63 %. Mp. = 527–528 K. ^{1}H NMR spectrum, δ, ppm: 3.88 s (3H, CH_3); 3.96 s (3H, CH_3); 7.13–7.15 m (1H, CH_{ar}); 7.32–7.36 m (2H, CH_{ar}); 7.76–7.87 m (2H, CH_{ar}); 8.07–8.09 m (1H, CH_{ar}); 8.21–8.23 m (1H, CH_{ar}). ^{13}C NMR spectrum, δ, ppm: 52.96, 53.29 (CH_3); 124.25, 126.47, 127.31, 127.98, 130.01, 132.29, 132.45, 133.86, 134.01, 134.35, 134.43, 136.50 (C_{ar}); 136.67, 144.81 (C-COOMe); 156.56, 159.73 (COO); 181.80, 182.22 (C=O). IR spectrum, ν, cm^{-1}: 1470 (N=N), 1667, 1646 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 392 [M+H] (98.7). Found, %: C 61.45; H 3.28; N 10.82. $C_{20}H_{13}N_3O_6$. Calculated, %: C 61.38; H 3.35; N 10.74.

Dimethyl 1-(9,10-dioxo-9,10-dihydroanthracen-2-yl)-1H-1,2,3-triazol-4-carboxylate 12. Prepared as compound **11**. Yield 61 %. Mp. = 531–533 K. ^{1}H NMR spectrum, δ, ppm: 3.88 s (3H, CH_3); 3.95 s (3H, CH_3); 7.52–7.53 (1H, CH_{ar}); 7.71–7.73 m (1H, CH_{ar}); 7.82–7.97 m (3H, CH_{ar}); 8.11–8.13 m (1H, CH_{ar}); 8.22–8.25 m (1H, CH_{ar}). ^{13}C NMR spectrum, δ, ppm: 52.97, 53.25 (CH_3); 117.24, 125.23, 126.43, 126.74, 128.59, 130.05, 133.06, 133.91, 134.32, 134.38, 134.45 (C_{ar}); 136.51 (C-COOMe); 141.13 (C-N); 144.17 (C-COOMe); 156.92, 160.21 (COO); 180.77, 182.36 (C=O). IR spectrum, ν, cm^{-1}: 1459 (N=N), 1674, 1637 (C=O quinone ring). LC-MS spectrum, m/z ($I_{rel.}$, %): 392 [M+H] (100). Found, %: C 61.32; H 3.41; N 10.65. $C_{20}H_{13}N_3O_6$. Calculated, %: C 61.38; H 3.35; N 10.74.

1,4-Bis(4-phenyl-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 15a. Yield 42 %. Mp. = 529––531 K. ^{1}H NMR spectrum, δ, ppm: 7.24–7.42 m (6H, CH_{ar}); 7.83–7.87 m (8H, CH_{ar}); 8.20–8.27 m (2H, CH_{ar}); 9.06 s (2H, CH=). ^{13}C NMR spectrum, δ, ppm: 123.23 (C_{ar}); 123.38 (2CH=) 127.13, 128.88, 130.07, 131.26, 133.69, 134.67 (C_{ar}), 149.16 (C-Ph); 181.32, 182.55 (C=O). IR spectrum, ν, cm^{-1}: 1483 (N=N), 1665, 1641 (C=O quinone ring). LC-MS spectrum, m/z ($I_{rel.}$, %): 495 [M+H] (93). Found, %: C 72.77; H 3.59; N 17.10. $C_{30}H_{18}N_6O_2$. Calculated, %: C 72.87; H 3.67; N 16.99.

Dimethyl 1,1'-(9,10-dioxo-9,10-dihydroanthracene-1,4-diyl)bis(1H-1,2,3-triazol-4-carboxylate) 15b. Yield 44 %. Mp. = 533–535 K. ^{1}H NMR spectrum, δ, ppm: 3.96 s (6H, CH_3); 7.71–7.76 m (2H, CH_{ar}); 8.41–8.46 m (2H, CH_{ar}); 8.76 m (1H, CH_{ar}); 9.83 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 52.49 (CH_3); 124.09, 127.22, 127.57, 131.98, 132.12, 133.64 (C_{ar}); 137.89 (C-COOMe); 160.58 (COOMe); 180.84, 181.81 (C=O). IR spectrum, ν, cm^{-1}: 1478 (N=N), 1682, 1643 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 459 [M+H] (89). Found, %: C 57.74; H 3.13; N 18.25. $C_{22}H_{14}N_6O_6$. Calculated, %: C 57.65; H 3.08; N 18.33.

1-Azide-4-(4-phenyl-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 16a. Yield 17 %. Mp. = 514––515 K. ^{1}H NMR spectrum, δ, ppm: 7.36–7.55 m (4H, CH_{ar}); 7.72–7.89 m (5H, CH_{ar}); 8.43–8.52 m (2H, CH_{ar}); 9.01 s (1H, CH=). ^{13}C NMR, δ, ppm: 120.29 (CH=); 122.78, 124.06, 126.15, 126.93, 127.59, 127.69, 127.98, 128.43, 128.59, 130.12, 132.65, 133.72, 133.91, 134.54, 135.44, 139.01 (C_{ar}); 149.16 (C-Ph); 181.83, 182.64 (C=O). IR spectrum, ν, cm^{-1}: 1483 (N=N), 1678, 1628 (C=O quinone ring), 2100 (N_3). LC-MS spectrum, m/z ($I_{rel.}$, %): 393 [M+H] (95). Found, %: C 67.46; H 3.01; N 21.56. $C_{22}H_{12}N_6O_2$. Calculated, %: C 67.34; H 3.08; N 21.42.

Methyl 1-(4-azide-9,10-dioxo-9,10-dihidroanthracene-1-yl)-1*H*-1,2,3-triazol-4-carboxylate) 16b. Yield 15 %. Mp. = 509–510 K. ^{1}H NMR spectrum, δ, ppm: 3.98 s (3H, CH_3); 7.83–7.85 m (1H, CH_{ar}); 8.01–8.12 m (1H, CH_{ar}); 8.43–8.61 (2H, CH_{ar}); 8.79–8.82 m (2H, CH_{ar}); 9.08 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 52.47 (CH_3); 120.35, 124.01, 126.23, 127.06, 127.43, 127.97, 128.56, 130.34, 132.76, 133.81, 134.02, 135.48, 139.31 (C_{ar}); 142.87 (CH = C); 160.49 (COO); 181.92, 182.39 (C=O). IR spectrum, ν, cm^{-1}: 1479 (N=N), 1685, 1627 (C=O quinone ring), 2110 (N_3). LC-MS spectrum, m/z (I_{rel}, %): 375 [M+H] (91). Found, %: C 57.86; H 2.61; N 22.53. $C_{18}H_{10}N_6O_4$. Calculated, %: C 57.76; H 2.69; N 22.45.

1,5-Bis(4-phenyl-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 17a. Yield 46 %. Mp. = 519–520 K. ^{1}H NMR spectrum, δ, ppm: 7.39–7.63 m (8H, CH_{ar}); 7.86–8.05 m (6H, CH_{ar}); 8.34–8.36 m (2H, CH_{ar}); 9.64 s (2H, CH=). ^{13}C NMR spectrum, δ, ppm: 122.88 (CH=); 124.95, 126.72, 126.82, 127.18, 128.81, 128.88, 130.01, 132.27, 135.41, 137.10 (C_{ar}), 149.21 (C-Ph); 180.46, 182.21 (C=O). IR spectrum, ν, cm^{-1}: 1476 (N=N), 1678,

1633 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 495 [M+H] (90). Found, %: C 72.96; H 3.54; N 16.89. $C_{30}H_{18}N_6O_2$. Calculated, %: C 72.87; H 3.67; N 16.99.

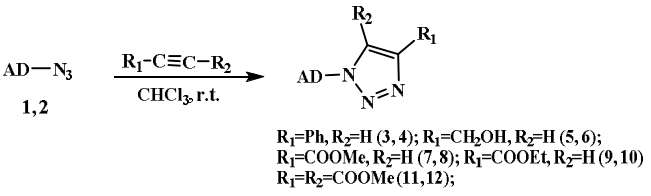
Dimethyl 1,1'-(9,10-dioxo-9,10-dihydroanthracen-1,5-diyl)bis(1*H*-1,2,3-triazol-4-carboxylate) 17b. Yield 41 %. Mp. = 527–529 K. ^{1}H NMR spectrum, δ, ppm: 3.88 s (3H, CH_3); 3.96 s (3H, CH_3); 7.85–7.91 m (4H, CH_{ar}); 8.20–8.25 m (2H, CH_{ar}); 9.21 s (2H, CH=). ^{13}C NMR spectrum, δ, ppm: 52.50 (CH_3); 125.54, 126.72, 127.03, 127.27, 132.65, 135.25, 138.12 (C_{ar}); 143.13 (C-COOMe); 160.55 (COOMe); 180.47, 181.93 (C=O). IR spectrum, ν, cm^{-1}: 1471 (N=N), 1668, 1638 (C=O quinone ring). LC-MS spectrum, m/z (I_{rel}, %): 459 [M+H] (89). Found, %: C 57.74; H 3.13; N 18.25. $C_{22}H_{14}N_6O_6$. Calculated, %: C 57.65; H 3.08; N 18.33.

1-Azide-5-(4-phenyl-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione 18a. Yield 16 %. Mp. = 520––522 K. ^{1}H NMR spectrum, δ, ppm: 7.42–7.64 m (4H, CH_{ar}); 7.82–8.10 m (6H, CH_{ar}); 8.31–8.34 m (1H, CH_{ar}); 9.09 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 122.68 (CH=); 122.88, 123.56, 123.62, 125.58, 125.78, 126.82, 127.32, 128.83, 128.88, 130.01, 134.22, 134.72, 134.91, 136.04, 136.59, 140.45 (C_{ar}); 149.29 (C-Ph); 181.92, 182.28 (C=O). IR spectrum, ν, cm^{-1}: 1475 (N=N), 1681, 1623 (C=O quinone ring), 2080 (N_3). LC-MS spectrum, m/z ($I_{rel.}$, %): 393 [M+H] (93). Found, %: C 67.31; H 3.12; N 21.37. $C_{22}H_{12}N_6O_2$. Calculated, %: C 67.34; H 3.08; N 21.42.

Methyl 1-(5-azide-9,10-dioxo-9,10-dihydroanthracen-1-yl)-1*H*-1,2,3-triazol-4-carboxylate) 18b. Yield 18 %. Mp. = 504–506 K. ^{1}H NMR spectrum, δ, ppm: 3.99 s (3H, CH_3); 7.79–7.82 m (4H, CH_{ar}); 8.14–8.17 m (1H, CH_{ar}); 8.21–8.24 m (1H, CH_{ar}); 9.07 s (1H, CH=). ^{13}C NMR spectrum, δ, ppm: 52.49 (CH_3); 122.74 (CH=) 123.56, 123.74, 125.53, 125.84, 127.02, 127.26, 134.55, 134.58, 136.59, 137.61, 140.45 (C_{ar}); 143.13 (C-COO); 160.51 (COOMe); 181.86, 182.47 (C = O). IR spectrum, ν, cm^{-1}: 1469 (N=N), 1680, 1629 (C=O quinone ring), 2096 (N_3). LC-MS spectrum, m/z (I_{rel}, %): 375 [M+H] (92). Found, %: C 57.71; H 2.75; N 22.52. $C_{18}H_{10}N_6O_4$. Calculated, %: C 57.76; H 2.69; N 22.45.

3. Results and Discussion

The new 1,2,3-triazole derivatives of 9,10-anthracendione **3-12** were obtained by the reaction of 1,3-dipolar azide-alkyne cycloaddition [1], which includes the interaction of freshly prepared azides AD-N_3 **1,2** [13, 14] (1,3-dipoles) with substituted acetylenes (dipolarofiles (Scheme 1, Table 1).



Scheme 1. Obtaining of the (1*H*-1,2,3-triazole-1(2)-yl)anthracene-9,10-diones **3-12**

The reaction of azides **1, 2** with phenylacetylene, propargyl alcohol and alkyl propiolates was carried out under conditions of copper(I)-catalyzed (CuAAC) reaction in the presence of trimethylamine. The reaction does not need the use of copper salts as catalyst in the case of interaction of **1, 2** with dimethyl acetylenedicarboxylate (Table 1). Target triazoles were obtained with the yields of 61–70 %.

Stepwise mechanism of the CuAAC reaction is realized through the formation of copper acetylide intermediate, in which copper atom has an activating effect on azide group by their coordination. It determines the regioselectivity of this reaction. Triethylamine, as was found in works [16-18], facilitates the formation of active copper-acetylide complex and passing of "click reaction". Then, six-membered metal cycle is formed, following reductive elimination with obtaining of copper-triazolyl derivative. The 1,2,3-triazole **3-10** is formed by dissociation [19].

The CuAAC reaction of 1,4- and 1,5-diazido-9,10-anthracendiones **13, 14** with phenylacetylene and methyl propiolate leads to the formation of bis-triazole derivatives **15a,b** and **17a,b**, which were isolated from the reaction mixture after chromatographic separation on silica gel (eluent – benzene:acetonitrile = 6: 1) with yields of 41–46 % (Scheme 2).

It should be noted that products of 1,3-dipolar addition of one azide group **16a,b** and **18a,b** (15–18 %), which contained only one 1,2,3-triazole cycle, were isolated together with major products bis-triazoles **15a,b** and **17a,b** by chromatographic column (Scheme 2). V. Rodionov *et al.* [20] observed a similar situation of simultaneous formation of bis-triazoles as major products and minor amounts of mono-triazoles under conditions of copper-catalysed reaction in the year 2005. Obviously, the formation of products of monoaddition of **16a,b** and **18a,b** indicates staging of passing of CuAAC reaction of two azide groups and causes by influence of quinonic conjugation in the molecule.

Table 1

The products of azide-alkyne cycloaddition 3-12

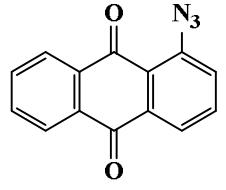
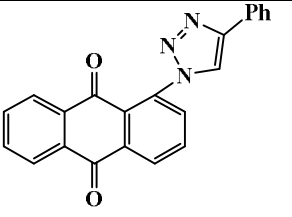
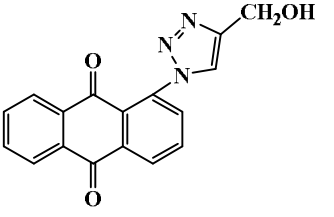
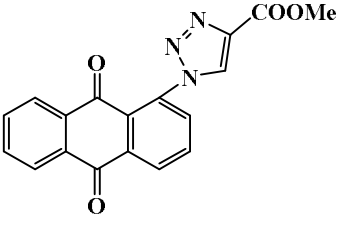
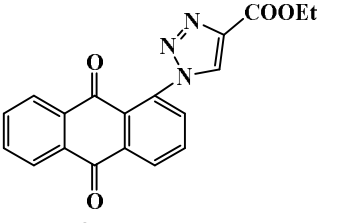
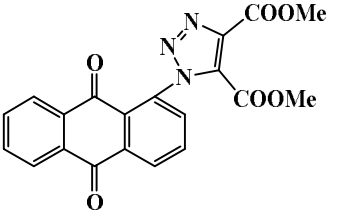
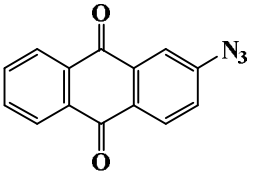
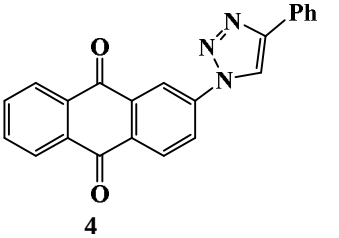
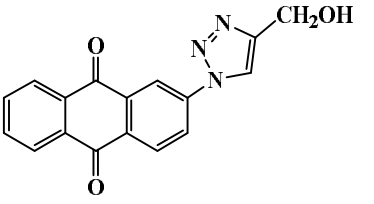
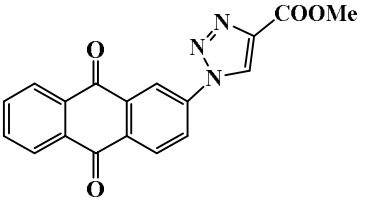
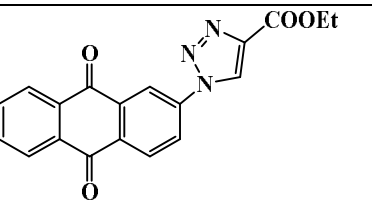
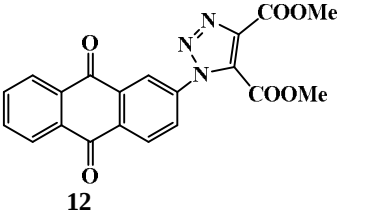
AD-N_3	Acetylene derivative	Catalyst	Product
1	2	3	4
 **1**	HC≡C-Ph	CuI	 **3**
	HC≡C-CH_2OH	CuI	 **5**
	HC≡C-COOMe	CuI	 **7**
	HC≡C-COOEt	CuI	 **9**
	MeOOC-C≡C-COOMe	-	 **11**
 **2**	HC≡CPh	CuI	 **4**

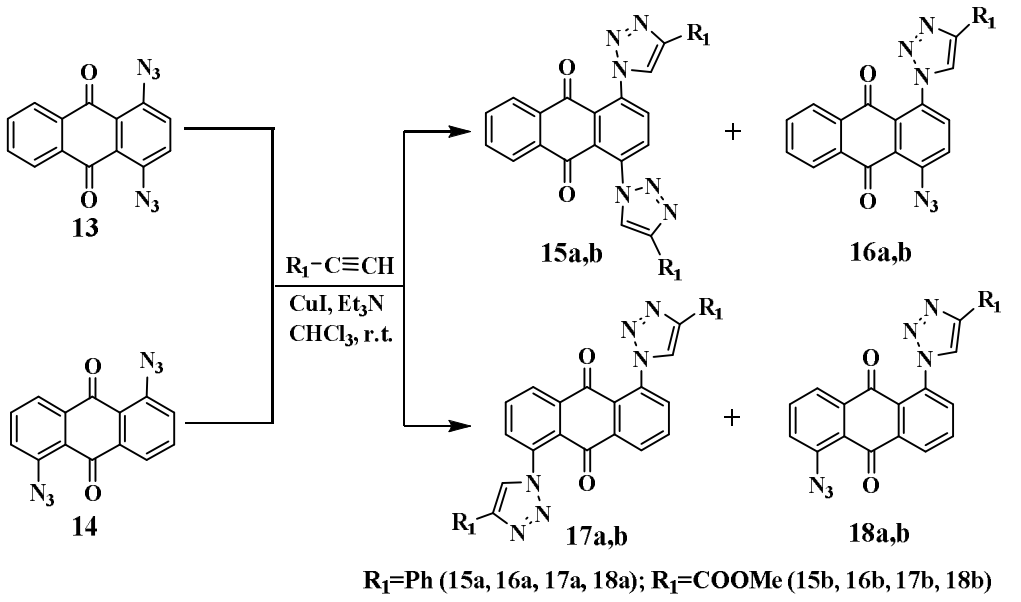
Table 1 (continued)

1	2	3	4
	HC≡C-CH_2OH	CuI	 **6**
	HC≡C-COOMe	CuI	 **8**
	HC≡C-COOEt	CuI	 **10**
	MeOOC-C≡C-COOMe	-	 **12**

The structure of triazoles **3-12**, **15-17** was confirmed by ^{1}H, ^{13}C NMR and LC-MS spectra. The signals of protons of 9,10-anthracenedione fragment and proton singlets of methine group of triazole cycle are observed in ^{1}H NMR spectra at 8.64-9.86 ppm. The signals of carbon atom of methine group of the 1,2,3-triazole fragment at 116.77–122.88 ppm and R_1-substituents are presented in ^{13}C NMR spectra. The disappearance of an intense band of stretching vibration of azide group at 2100–2120 cm^{-1} and the appearance of absorption bands -N=N- at 1414-1483 cm^{-1} in IR spectra confirms the formation of triazole cycle in compounds **3-12**, **15-17**. A broad absorption band at 2500–3200 cm^{-1}, characteristic of hydroxy-group stretching vibration band of hydroxymethyl fragment, is presented in the IR spectra of triazoles **5** and **6**. A strong stretching vibration bands of azide group at 2080–2110 cm^{-1} and absorption bands -N=N- of triazole cycle within 1469-1483 cm^{-1} are in IR spectra of mono-triazole derivatives **16a,b** and **18a,b**. Their ^{1}H and ^{13}C NMR spectra are characterized by signal of methine group of triazole fragment at 9.01–9.09 ppm and 120.29–122.74 ppm, respectively. Peaks of corresponding molecular ions of target products are observed in LC-MS spectra of synthesized triazoles.

Approach *in silico* has been used to continue preliminary results of correlation "structure-prediction computer-experimental studies" [8, 12] and to identify the most promising directions of experimental studies of new functionalized 1(2)amino-9,10-anthracendiones with triazole fragment. It included a prediction of possible pharmacological activity by the program *PASS Online* [21] and determination of mechanisms for possible implementation of biological activity using a software package *Schrödinger Suite 2014* [22].

Promising experimental studies for antitumor and anti-inflammatory activity and possible mechanisms of realization of their action have been shown by the computer screening for triazoles **3-12**, **15** and **17** using *PASS Online* (Pa>0.5). The results of prediction of spectrum of probable biological activity are summarized in Table 2.



Scheme 2. Interaction of 1,4- and 1,5-diazido-9,10-anthracendiones **13,14** with phenylacetylene and methyl propiolate

Table 2

Predicted biological activity of 1,2,3-triazole derivatives 3-12, 15, 17 (Pa > 0.5)

compound / action	3a	4b	5a	6b	7a	8b	9a	10b	11a	12b	15a	15b	17a	17b
Antineoplastic	0.750	0.672	0.674	0.589	0.722	0.653	0.615	0.528	0.567	–	0.756	0.735	0.756	0.735
Antiinflammatory	0.601	0.563	0.614	0.586	–	–	–	–	–	–	0.612	–	0.612	–
CYP2H substrate	–	–	–	–	0.643	0.643			0.683	0.683	–	0.651	–	0.651
Membrane permeability inhibitor	–	–	–	–	0.543	0.543	0.580	0.580	0.575	0.575	–	0.563	–	0.563
5-O-(4-coumaroyl)-D-quinate 3'-monooxygenase inhibitor	0.707	0.760	0.700	0.753	0.635	0.696	0.822	0.857	0.697	0.751	0.715	0.647	0.715	0.647

Table 3

Glide Maestro results in phase XP

Compound	6	5	4	3	8	10	17a	7	Imatinib
Docking score	-9.317	-8.707	-8.521	-8.001	-7.998	-7.748	-7.553	-7.383	-7.263

We have carried out the molecular docking for new 9,10-anthracendiones functionalized with 1,2,3-triazole fragment by the software package *Schrödinger Suite 2014* to implement mechanisms of antitumor activity. The process of docking consisted of the following steps:

– protein selection and preparation (target protein);

– selection of target protein; crystallographic structure was retrieved from the Protein Data Bank (PDB) [23];

– preparation of target protein using Protein Preparation Wizard with removing water molecules which do not form hydrogen bonds, following from which, bond orders were assigned and hydrogen atoms were added to the structure of the protein-target from PDB file;

– optimization of the protein structure at pH 7.0 using wizard PROBKA;

– minimization of the protein structure using OPLS-2005 force field;

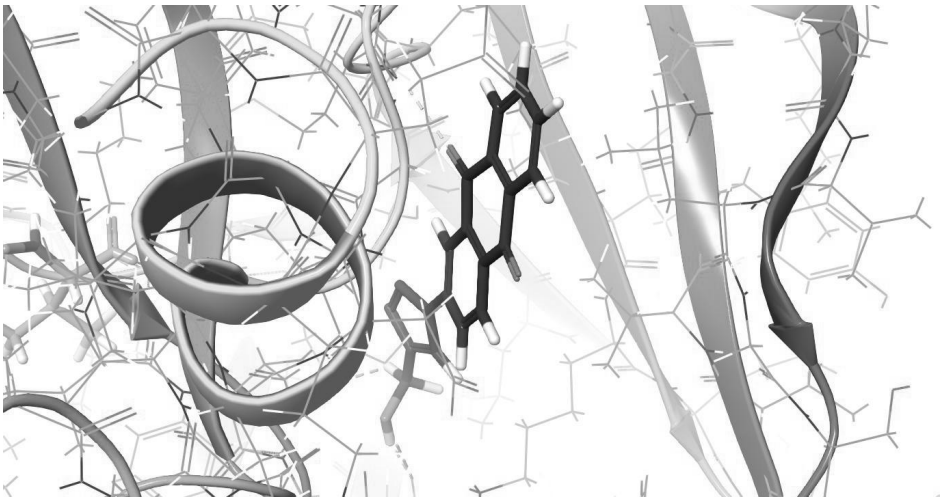


Fig. 1. Visualization of binding of compound 2-(4-(hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione **6b** in the protein zone 1M17

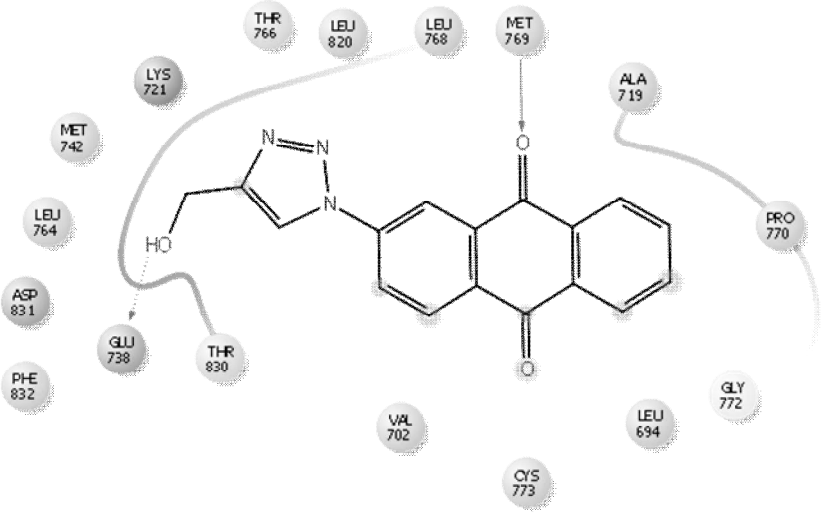


Fig. 2. Types of interactions of compound 2-(4-(hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione **6b** in binding range with the target protein 1M17

– ligand preparation using LigPrep wizard by assigning the bond orders and bond angles with subsequent minimization of OPLS-2005 force field. For accurate enumeration of ligand protonation states in biological conditions we used Epik;

– generation of Grid box of ligand and receptor using Receptor Grid Generation of Glide Maestro.

– virtual screening Glide Maestro in phase XP.

Receptor protein-tyrosine kinases EGFR (1NQL, 1IVO, 1M17, 2GS6) and PDGF (1T46), non-receptor tyrosine kinases SRC (1SKJ) and non-specific tyrosine kinases ABL (3OXZ, 3QRJ, 2ABL) were the objects of docking evaluations. Compounds with medium and lower affinity among the investigated compounds according to the obtained data of the scoring function were identified. However, the highest binding (-7.3)–(-9.3) was observed to the family of receptor tyrosine kinases of epidermal growth factor EGFR (protein code 1M17) (Table 3).

The molecule of investigated 2-(4-(hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione **6b** has scoring function G_{score} = -9.3. It indicates a high level of their binding to protein zone 1M17 (Imatinib was standard ligand). Fig. 1 shows the visualization of this interaction.

2-(4-(Hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione **6b** is in a hydrophobic pocket (Fig. 2) formed by amino acid residues of leucine (LEU:820, LEU:768, LEU:694, LEU:764), methionine (MET:769, MET:742), alanine (ALA:719), proline (PRO:770), cysteine (CYS:773), valine (VAL:702), phenylalanine

(PHE:832), asparagic acid (ASP:831), glutamic acid (GLU:738) and lysine (LYS:721). The molecule of 2-(4-(hydroxymethyl)-1*H*-1,2,3-triazole-1-yl)anthracene-9,10-dione **6b** forms a hydrogen bond between the hydrogen atom of the hydroxy group of CH_2OH fragment of triazole ring and polar amino acid residue GLU:738 of main peptide chain.

It can be concluded that inhibition of tyrosine kinase of epidermal growth factor by binding with the active zone of protein 1M17 due to hydrogen bond with polar amino acid residue GLU:738 and binding of the ligand molecule in the hydrophobic region of the protein target by pharmacophore fragments of 1,2,3-triazole group and 9,10-antracenedione is the probable mechanism of implementing of anticancer activity.

The obtained data show that the search of anticancer agents in this class of compounds by modifying of ligand with other pharmacophore fragments using molecular docking to biological targets of pathological process is promising.

4. Conclusions

For the first time a series of new promising biologically active compounds, including 9,10-anthracenedione and 1,2,3-triazole pharmacophore fragments in their structure, has been obtained by the reaction of 1,3-dipolar cycloaddition of azides and alkynes. It was found that bis- and mono-triazole derivatives are obtained by cycloaddition reaction of 1,4(1,5)-diazido-9,10-anthracendiones with phenylacetylene and methyl propiolate. Promising areas of experimental research for new triazole derivatives of 9,10-anthracendione, in particular for anticancer and anti-inflammatory activity, has been shown by computer screening using the program *PASS Online*. Compounds with high affinity to the family of receptor tyrosine kinases of the epidermal growth factor receptor EGFR have been found among newly synthesized 1,2,3-triazole derivatives of 9,10-anthracendione using molecular docking. Results of docking indicate a probable mechanism for the implementation of antitumor activity.

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НОВІ 1,2,3-ТРИАЗОЛІЛАНТРАЦЕН-9,10-ДІОНИ: СИНТЕЗ ТА КОМП'ЮТЕРНИЙ СКРИНІНГ БІОАКТИВНОСТІ

Анотація. *Досліджено реакції 1,4(1,5)-діазидо-9,10-антрацендіонів із фенілацетиленом та метиловим естером ацетиленкарбонової кислоти за умов купрум(I)-каталізованої реакції азид-алкінового циклоприєднання та одержано ряд нових 1,2,3-триазолільних похідних 9,10-антрацендіону. Для визначення напрямків експериментальних біомедичних досліджень синтезованих сполук проведено комп'ютерний скринінг програмою PASS Online. Молекулярний докінг нових синтезованих 1,2,3-триазолів 9,10-антрацендіону виявив сполуки з високим ступенем афінітету до сімейства рецепторних тирозинкіназ епідермального фактору росту EGFR, що може свідчити про ймовірний механізм реалізації протипухлинної активності.*

Ключові слові: *1(2)-азидо-9,10-антрацендіони; 1,4(1,5)-діазидо-9,10-антрацендіони, ацетилени, 1,3-диполярне циклоприєднання, 1,2,3-триазоли, комп'ютерний скринінг.*