ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Synthesis of New Fused Tricyclic Quinoid Systems and Studying of Their Biological Activity *In-Silico*

Yuliia Dumanska[1], Yurii Shakh[1], Anastasiia Kudrinetska[1], Khrystyna Bolibrukh[1], Andrii Karkhut[1], Bohdan Lytvyn[1], Oleksii Kovalchuk[1], Olha Marshalok[2], Mykola Platonov[3], Sviatoslav Polovkovych[1]*, and Volodymyr Novikov[1]

[1]Department of Technology of Biologically Active Substances, Pharmacy and Biotechnology, National University "Lviv Polytechnic", 79013, Ukraine, Lviv,Bandera Str., 12
[2]Department of General, Bioinorganic, Physical and Colloidal Chemistry, Lviv national medical university, 79010, Ukraine, Lviv, Pekarska Str., 52
[3]Department of Chemistry, Army Academy named after Hetman Petro Sahaydachnyi , 79012, Lviv, Gwardiyska str., bld. 32

ABSTRACT

Interaction between 5-R-substituted derivatives of 1,4-naphthoquinone and 2,3-dimethylbutadiene was carried out by Diels-Alder reaction. Using computer system PASS opportunity of displaying biological activity of the synthesized compounds was established. The basic ways of modifying the synthesized products to increase their biological activity were developed.
Keywords: 1,4-quinones, 2,3-dimethylbutadiene, Diels-Alder reaction.

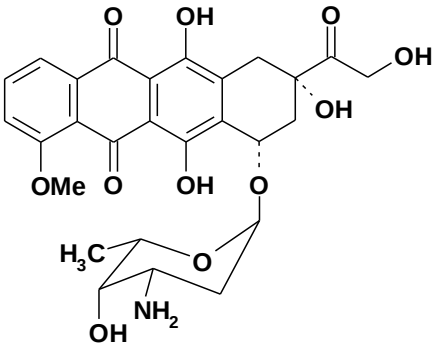
Corresponding author

ISSN: 0975-8585

INTRODUCTION

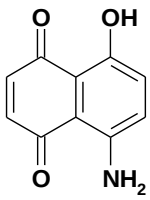
Research work on searching, synthesis and studying of properties of 5-substituted 1,4-naphthoquinones and their derivatives has already been carried out during more than half of the century, and have been confirmed by the results of numerous scientists [1-8].

Among the existing drugs, 5-substituted 1,4-naphthoquinone is the basis of the molecule of antibiotic adriamycin **(1)**, which possesses antitumor activity [4].

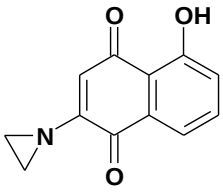


1

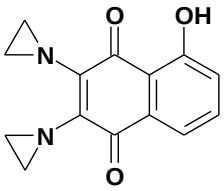
A number of 1,4-naphthoquinone derivatives has been investigated on cancer cell lines by Roger M. Phillips and co-workers. Some of the compounds **(2-5)** showed high antitumor activity. These studies were a continuation of the study of indolquinone bioreductive compound **(6)** [7].



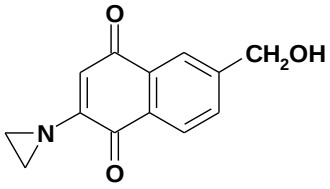
2



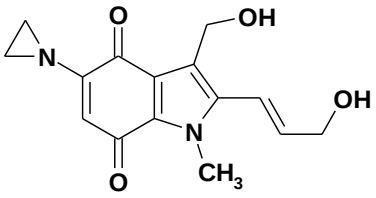
3



4



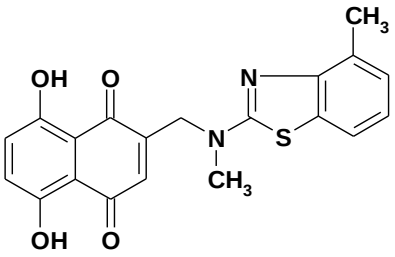
5



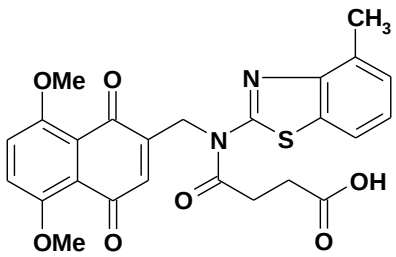
6

Korean scientists have carried out the research in the synthesis and study of antitumor activity *in vivo* of some derivatives of 1,4-naphthoquinone **(7-9)**. The results confirmed the promising usage of 1,4-naphthoquinone derivatives as anticancer agents that effectively inhibit DNA topoisomerase [8].

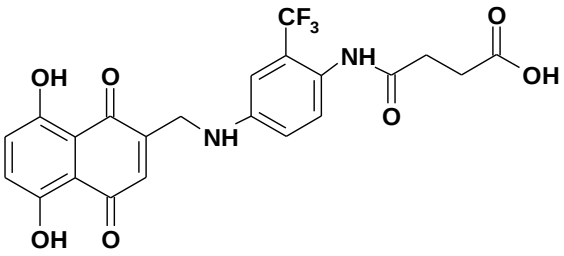
ISSN: 0975-8585



7



8



9

There are many well-known 1,4-naphthoquinone derivatives that show antibacterial, antifungal and antiviral activities [9-18]. Many of them are promising objects for studying of their anticancer activity through the mechanism of DNA intercalation [19-21].

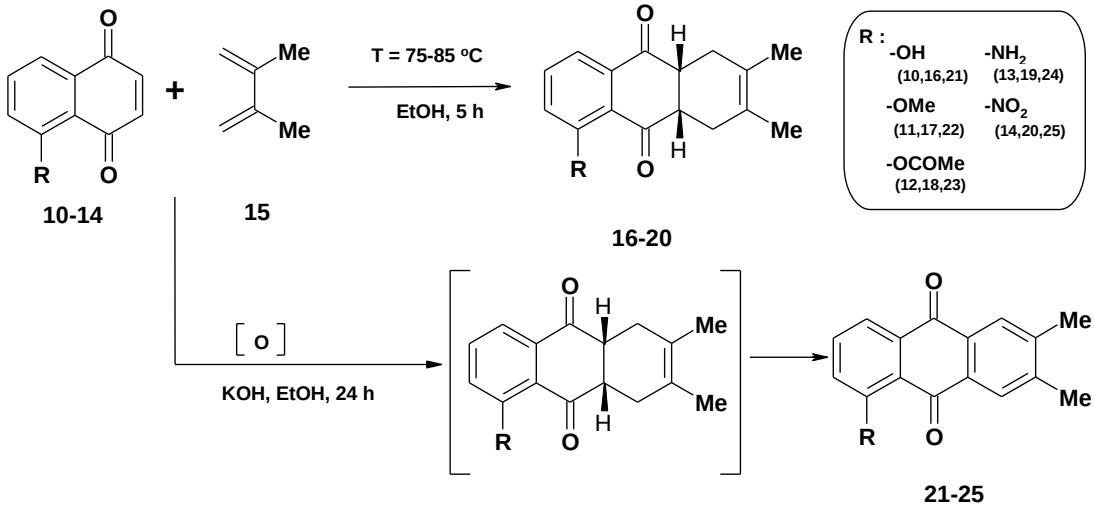
A number of natural derivatives of 1,4-quinones, which were isolated from microorganisms, fungi, higher plants and animals, are known. A wide range of biological activities that these compounds are showing causes the development of new methods for obtaining their synthetic analogues and similar systems. Also the important task is the synthesis of both, simple and complex, molecules of 1,4-naphthoquinone derivatives in order to search among them effective drugs with directed biological activity.

RESULTS AND DISCUSSION

The aim of obtaining quinoid fused tricyclic systems as initial building blocks for further construction on their basis drug similar molecules by reaction between 5-R-substituted derivatives of 1,4-naphthoquinone and 2,3-dimetylbutadiene was set. Synthesis of compounds was carried out by Diels-Alder reaction between dienophiles, such as 5-hydroxy-1,4-naphthoquinone **(10)**, 5-methoxy-1,4-naphthoquinone **(11)**, 5-acetoxy-1,4-naphthoquinone **(12)**, 5-amino-1,4-naphthoquinone **(13)**, 5-nitro-1,4-naphthoquinone **(14)** and diene – 2,3-dimetylbutadiene **(15)**. The reaction was carried out in two stages for obtaining systems with saturated bond **(16-20)** and fully unsaturated tricyclic molecules **(21-25)** (Figure 1).

ISSN: 0975-8585

Figure 1



In this way we have obtained a number of building frames for a further series of compounds that exhibit biological activity through their modification by several reaction centers, namely:

Halogenation reaction of the methyl groups in the 2 and 3 position with a following dehydrohalogenation. Obtained dienes by reaction with quinone derivatives as dienophiles form polycyclic systems that have promising biological activity;

Reactions of alkylation and acylation of amino group in the 5 position of the corresponding derivatives of 1,4-naphthoquinone **(13, 19, 24)**.

Thus, established combinatorial library of 1,4-quinone derivatives enables to select biological targets by ligand-directed virtual screening using PASS [22-25].

List of predicted biological activity by program PASS. TABLE 1.

№	Pa	Pi	ACTIVITIES
16	0,929	0,006	CYP2C12 substrate
	0,874	0,010	Ubiquinol-cytochrome-c reductase inhibitor
	0,857	0,009	Antiseborrheic
	0,848	0,011	CYP2J substrate
	0,734	0,020	Antineoplastic
17	0,883	0,016	CYP2C12 substrate
	0,815	0,013	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,824	0,025	Ubiquinol-cytochrome-c reductase inhibitor
	0,824	0,027	Aspulvinone dimethylallyltransferase inhibitor
	0,752	0,034	CYP2J substrate
	0,716	0,023	Antineoplastic
18	0,888	0,005	Antiseborrheic
	0,842	0,026	CYP2C12 substrate
	0,811	0,018	CYP2J substrate
	0,777	0,023	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,766	0,015	TP53 expression enhancer
	0,737	0,011	Oxidoreductase inhibitor
	0,744	0,019	Antineoplastic
	0,743	0,053	Ubiquinol-cytochrome-c reductase inhibitor

	0,788	0,007	CYP2B substrate
	0,801	0,021	CYP2J substrate
	0,726	0,007	CYP1A1 substrate
19	0,738	0,020	Antineoplastic
	0,737	0,043	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0,719	0,062	Ubiquinol-cytochrome-c reductase inhibitor
	0,703	0,057	CYP2C12 substrate
	0,856	0,015	Ubiquinol-cytochrome-c reductase inhibitor
	0,781	0,026	CYP2J substrate
	0,759	0,008	CYP2B substrate
	0,741	0,006	CYP1A1 substrate
20	0,743	0,016	Lysase inhibitor
	0,735	0,035	Acrocylindropepsin inhibitor
	0,735	0,035	Chymosin inhibitor
	0,735	0,035	Saccharopepsin inhibitor
	0,705	0,038	Polyporopepsin inhibitor
	0,709	0,052	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0,926	0,007	CYP2C12 substrate
	0,896	0,012	Membrane integrity agonist
	0,886	0,008	Ubiquinol-cytochrome-c reductase inhibitor
	0,873	0,003	Alkane 1-monooxygenase inhibitor
	0,871	0,015	Aspulvinone dimethylallyltransferase inhibitor
	0,848	0,010	Antiseborrheic
	0,838	0,006	NAD(P)+-arginine ADP-ribosyltransferase inhibitor
	0,834	0,003	Histidine kinase inhibitor
21	0,840	0,012	CYP2J substrate
	0,834	0,014	Chlordecone reductase inhibitor
	0,810	0,009	Aldehyde oxidase inhibitor
	0,819	0,021	Testosterone 17beta-dehydrogenase (NADP+) inhibitor
	0,785	0,012	TP53 expression enhancer
	0,778	0,014	Membrane permeability inhibitor
	0,766	0,005	UGT1A9 substrate
	0,775	0,015	Antineoplastic
	0,764	0,004	Pin1 inhibitor
	0,876	0,017	CYP2C12 substrate
	0,862	0,017	Aspulvinone dimethylallyltransferase inhibitor
	0,847	0,025	Membrane integrity agonist
22	0,841	0,019	Ubiquinol-cytochrome-c reductase inhibitor
	0,813	0,014	Gluconate 2-dehydrogenase (acceptor) inhibitor
	0,784	0,004	Carminative
	0,759	0,017	Antineoplastic
	0,762	0,027	Chlordecone reductase inhibitor
	0,881	0,006	Antiseborrheic
	0,832	0,028	CYP2C12 substrate
23	0,803	0,020	CYP2J substrate
	0,788	0,012	TP53 expression enhancer
	0,803	0,035	Membrane integrity agonist
	0,780	0,014	Antineoplastic
	0,779	0,005	3-Hydroxybenzoate 6-monooxygenase inhibitor
24	0,792	0,023	CYP2J substrate
	0,777	0,015	Antineoplastic
	0,746	0,052	Ubiquinol-cytochrome-c reductase inhibitor
	0,870	0,011	Ubiquinol-cytochrome-c reductase inhibitor
	0,764	0,006	3-Hydroxybenzoate 6-monooxygenase inhibitor
	0,772	0,028	CYP2J substrate
25	0,759	0,029	Acrocylindropepsin inhibitor
	0,759	0,029	Chymosin inhibitor
	0,759	0,029	Saccharopepsin inhibitor
	0,741	0,014	Glucan endo-1,6-beta-glucosidase inhibitor

According to the results of the *in silico* prediction of biological activity by program PASS of the number of synthesized compounds we can conclude that general for almost all compounds (except 20, 25) is an antineoplastic activity, which can be realized by inhibiting the action of several enzymes (Ubiquinol-cytochrome-c reductase, Gluconate 2-dehydrogenase (acceptor), Aspulvinone dimethylallyltransferase, Oxidoreductase, Testosterone 17beta-dehydrogenase (NADP+), NAD(P)+-arginine ADP-ribosyltransferase, Histidine kinase, Membrane permeability) and binding of substrates (CYP2C12, CYP2J, CYP2B, SYP1A1, UGT1A9).

Thus, the determined probability of displaying antineoplastic activity provides an opportunity to study and implement a modification of the synthesized compounds to enhance biological effects.

The next stage of our work will be *in silico* studies, including selection of biotargets and their crystallographic models for implementation of receptor-directed molecular docking using the software package «OpenEye Scientific Software», expansion of combinatorial libraries and searching of substances with the highest degree of affinity.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a spectrometer ,,Varian VXR'' (300 MHz) (^{1}H chemical shifts are expressed in δ-scale relative to internal standard - tetramethylsilane as integrated intensities correspond to the allocation made.) Elemental analysis performed on a standard equipments for microanalysis. Monitoring the progress of the reaction and the identity of substances TLC was performed on plates "Silufol UV-254" and "Merk Kieselgel 60 F254". In determining the melting temperature correction for speaker connections column of mercury was undertaken.

(4aS,9aR)-5-hydroxy-2,3-dimethyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione (16)

To 0,68 g (0,0039 mol) 5-hydroxy-1,4-naphthoquinone dissolved in 10 ml of ethanol was added 0.32 g (0.0039 mol) of 2,3-dymetylbutadiene. The reaction mixture was heated for 5 hours with stirring under reflux. Then the solution was cooled and frozen within 10-12 hours. The product is in the form of white crystals was filtered and washed by ethanol [26]. Yield 81%, mp=193^{0}C. IR (KBr), cm^{-1}: 1720, 1680 (C=O), 1230 (OH). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7,63 (t, J=7,80; 7,71 Hz, 1H, CH-arom.); 7,56 (m, 1H, CH-arom.); 7,17 (dd, J=7,71; 1,44 Hz, 1H, CH-arom.); 3,36 (m, 1H, CH); 3,26 (m, 1H, CH); 2,21 (m, 4H, $2CH_2$); 1,65 (s, 6H, $2CH_3$). Calcd for ($C_{16}H_{16}O_3$), %: C=74.98 H=6.29. Found, %: C=75.15, H=6.41.

(4aS,9aR)-5-methoxy-2,3-dimethyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione (17)

Yield 82%, mp=201^{0}C. IR (KBr), cm^{-1}: 2830 (OCH_3), 1720, 1680 (C=O). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7,69 (m, 1H, CH-arom.);7,64 (t, J=8,14; 7,80 Hz, 1H, CH-arom.); 7,40 (dd, J=8,14; 1,44 Hz, 1H, CH-arom.); 3,94 (s, 1H, OCH_3); 3,37 (m, 1H, CH); 3,29 (m, 1H, CH); 2,21 (m, 4H, $2CH_2$); 1,65 (s, 6H, $2CH_3$). Calcd for ($C_{17}H_{18}O_3$), %: C=75.53, H=6.71. Found, %: C=75.35, H=6.40.

(8aS,10aR)-6,7-dimethyl-9,10-dioxo-5,8,8a,9,10,10a-hexahydroanthracen-1-yl acetate (18)

Yield 80%, mp=211^{0}C. IR (KBr), cm^{-1}: 1710, 1685 (C=O), 1370 ($OCOCH_3$). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7,75 (m, 1H, CH-arom.); 7,71 (t, J=7,90; 7,80 Hz, 1H, CH-arom.); 7,53 (dd, J=7,90; 1,44 Hz, 1H, CH-arom.); 3,40 (m, 1H, CH); 3,08 (m, 1H, CH); 2,25 (m, 4H, $2CH_2$); 2,44 (s, 1H, $COCH_3$); 1,65 (s, 6H, $2CH_3$). Calcd for ($C_{18}H_{18}O_4$), %: C=72.47, H=6.08. Found, %: C=72.35, H=6.38.

(4aS,9aR)-5-amino-2,3-dimethyl-1,4,4a,9a-tetrahydroanthracene-9,10-dione (19)

Yield 85%, mp=198^{0}C. IR (KBr), cm^{-1}: 3400 (NH_2), 1700, 1690 (C=O). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 7,87 (s, 2H, NH_2); 7,52 (m, 1H, CH-arom.); 7,47 (t, J=7,87; 7,73 Hz, 1H, CH-arom.); 6,96 (dd, J=7,87; 1,60 Hz, 1H, CH-arom.); 3,32 (m, 1H, CH); 3,04 (m, 1H, CH); 2,22 (m, 4H, $2CH_2$); 1,65 (s, 6H, $2CH_3$). Calcd for ($C_{16}H_{17}NO_2$), %: C=75.27, H=6.71, N=5.49. Found, %: C=75.14, H=6.39, N=5,36.

(4aS,9aR)-2,3-dimethyl-5-nitro-1,4,4a,9a-tetrahydroanthracene-9,10-dione (20)

Yield 74%, mp=220^{0}C. IR (KBr), cm^{-1}: 1705, 1685 (C=O), 1490 (NO_2). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,16 (dd, J=7,50; 2,00 Hz, 1H, CH-arom.); 8,02 (m, 1H, CH-arom.); 7,47 (t, J=7,50; 7,73 Hz, 1H, CH-arom.); 3,38 (m, 1H, CH); 3,33 (m, 1H, CH); 2,27 (m, 4H, $2CH_2$); 1,65 (s, 6H, $2CH_3$). Calcd for ($C_{16}H_{15}NO_4$), %: C=67.36, H=5.30, N=4.91. Found, %: C=67.16, H=5.19, N=4,75.

5-hydroxy-2,3-dimethyl-1,4-dihydroanthracene-9,10-dione (21)

To 0,68 g (0,0039 mol) 5-hydroxy-1 ,4-naphthoquinone dissolved in 10 ml of ethanol was added 0.32 g (0.0039 mol) of 2,3-dymetylbutadiene. The reaction mixture was heated for 5 hours with stirring under reflux. Then the solution was cooled and frozen within 10-12 hours. The product is in the form of white crystals was filtered and washed by ethanol.

For the reaction of dehydrogenation 0.81 g of adduct was dissolved in 12 ml of 5% spirituous KOH solution in three-neck flask with reflux and missed the air for 24 hours. Yellow product was filtered and washed by 4 ml water, 2 ml of ethanol and 1 ml of ether [26].

Yield 85%, mp=243^{0}C. IR (KBr), cm^{-1}: 1730, 1690 (C=O), 1240 (OH). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,17 (s, 1H, CH-arom.); 8,12 (s, 1H, CH-arom.); 7,82 (t, J=7,71; 7,76 Hz, 1H, CH-arom.); 7,75 (dd, J=7,76; 1,18 Hz, 1H, CH-arom.); 7,41 (dd, J=7,71; 1,18 Hz, 1H, CH-arom.); 2,40 (s, 6H, $2CH_3$). Calcd for ($C_{16}H_{12}O_3$), %: C=76.18 H=4.79. Found, %: C=76.03, H=4.65.

5-methoxy-2,3-dimethyl-1,4-dihydroanthracene-9,10-dione (22)

Yield 82%, mp=249^{0}C. IR (KBr), cm^{-1}: 2840 (OCH_3), 1710, 1680 (C=O). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,07 (s, 2H, 2CH-arom.); 7,81 (t, J=8,14; 7,76 Hz, 1H, CH-arom.); 7,74 (dd, J=7,76; 1,04 Hz, 1H, CH-arom.); 7,58 (dd, J=8,14; 1,04 Hz, 1H, CH-arom.); 3,98 (s, 1H, OCH_3);

2,40 (s, 6H, $2CH_3$). Calcd for ($C_{17}H_{14}O_3$), %: C=76.68, H=5.30. Found, %: C=76.51, H=5.22.

6,7-dimethyl-9,10-dioxo-5,8,9,10-tetrahydroanthracen-1-yl acetate (23)

Yield 84%, mp=260^{0}C. IR (KBr), cm^{-1}: 1720, 1680 (C=O), 1380 ($OCOCH_3$). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,25 (dd, J=7,76; 1,20 Hz, 1H, CH-arom.); 8,13 (s, 1H, CH-arom.); 8,07 (s, 1H, CH-arom.); 7,99 (t, J=7,90; 7,76 Hz, 1H, CH-arom.); 7,67 (dd, J=7,90; 1,20 Hz, 1H, CH-arom.); 2,45 (s, 1H, $COCH_3$); 2,40 (s, 6H, $2CH_3$). Calcd for ($C_{18}H_{14}O_4$), %: C=73.46, H=4.79. Found, %: C=73.60, H=4.72.

5-amino-2,3-dimethyl-1,4-dihydroanthracene-9,10-dione (24)

Yield 83%, mp=248^{0}C. IR (KBr), cm^{-1}: 3410 (NH_2), 1700, 1680 (C=O). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,11 (s, 1H, CH-arom.); 8,07 (s, 1H, CH-arom.); 7,72 (s, 2H, NH_2); 7,61 (t, J=7,87; 7,60 Hz, 1H, CH-arom.); 7,54 (dd, J=7,60; 1,60 Hz, 1H, CH-arom.); 7,18 (dd, J=7,87; 1,60 Hz, 1H, CH-arom.); 2,40 (s, 6H, $2CH_3$). Calcd for ($C_{16}H_{13}NO_2$), %: C=76.48, H=5.21, N=5.57. Found, %: C=76.70, H=5.19, N=5,53.

2,3-dimethyl-5-nitro-1,4-dihydroanthracene-9,10-dione (25)

Yield 80%, mp=270^{0}C. IR (KBr), cm^{-1}: 1720, 1690 (C=O), 1500 (NO_2). ^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,28 (dd, J=7,50; 2,00 Hz, 1H, CH-arom.); 8,12 (dd, J=7,50; 2,00 Hz, 1H, CH-arom.); 8,05 (s, 1H, CH-arom.); 8,01 (s, 1H, CH-arom.); 7,51 (t, J=7,50; 7,50 Hz, 1H, CH-arom.); 3,47 (m, 2H, CH_2); 3,28 (m, 2H, CH_2); 2,40 (s, 6H, $2CH_3$). Calcd for ($C_{16}H_{11}NO_4$), %: C=68.32, H=3.94, N=4.98. Found, %: C=68.20, H=3.97, N=4,95.

ACKNOWLEDGEMENTS

Work performed under the grant of the President of Ukraine to support young scientists F49-2013.

REFERENCES

[1] JW Macleod , RH Thomson. J Org Chem 1960;25 (1):36–42.
[2] J David Turnbull and et al. Biochemistry Pharmacology, Vol. 20, pp. 1383-1391.
[3] Wayne B Manning. Tetrahedron Lett. 19:1661-1664.
[4] T Ross Kelly and et al. JACS / 99:16 / August 3, 1977.
[5] Melvin D. Rozeboom, Inga-Mai Tegmo-Larsson, and K. N. Houk. J Org Chem 1981;46: 2338-2345.
[6] George A Kraus and Junwon Kim. J Org Chem 2002;67:2358-2360.
[7] Roger M. Phillips, Mohammed Jaffar, Derek J. Maitland. Biochem Pharmacol 2004; 68:2107–2116.
[8] Yongseog Chung, Jikang Yoo et al. Bull Korean Chem Soc 2007;28(4):691.
[9] Francesco Fringuelli. The Diels-Alder Reaction: Selected Practical Methods. – John Wiley &Sons 2002; 340.
[10] KS Lin, ML Debnath, CA Mathis, W Klunk. Bioorg Med Chem Lett 2009;19:2258 - 2262.
[11] K Serdons, et al. Eur J Med Chem 2009;44:1415-1426.

ISSN: 0975-8585

[12] G Turan-Zitouni, S Demirayak, ZA Kaplancikli, MT Yildiz. Eur J Med Chem. 2003;39: 267–272.
[13] ST Huang, IJ Hsei, C Chen. Bioorg Med Chem 206;14:6106-6119.
[14] CJ Lion, CS Matthews, G Wells, TD Bradshaw, MFG Stevens, AD Westwell. Bioorg Med Chem Lett 2006;16:5005-5008.
[15] N Siddiqui, SN Pandeya, SA Khau, J Stables, A Rana, M Alam, Md F Arshad, MA Bhat. Bioorg Med Chem 2007;17:255-259.
[16] F Russo, G Romeo, NA Santagati, A Caruso, V Cutuli, D Amore. Eur J Med Chem 1994;29: 569-578.
[17] F Russo, M Santagati. Farmaco Ed Sci 1976;31:41-48.
[18] JH Musser, RE Brown, B Love, K Baily, H Jones, R Kahen, F Haung, A Khandwala, M Leibowitz. J Med Chem 1984;27:121-125.
[19] S Polovkovych, G Zagoriy, O Bondarchuk, R Vynnytska, et al., Res J Pharm Biol Chem Sci, 2013, Vol. 4, Issue 2, 128-144.
[20] Bruce Armitage, Troels Koch, Henrik Frydenlund1, Gary B Schuster. Nucleic Acids Res 1998; 26(3):715–720.
[21] David T Breslin, et al. J Am Chem Soc. 1997;119:5043-5044.
[22] Geronikaki A, Druzhilovsky D, Zakharov A, Poroikov V. SAR QSAR Environ Res 2008 19(1-2):27-38.
[23] Lagunin A, Filimonov D, Poroikov V. Curr Pharm Des 2010;16(15):1703-17.
[24] VV Poroikov et al. J Chem Inform Comput Sci 2000;40:1349–1355.
[25] http://www.ibmc.msk.ru/PASS (accessed August 2009).
[26] CFH Allen and Alan Bell. Organic Syntheses Coll 1955;3:310.