ЕҢБЕК ҚЫЗЫЛ ТУ ОРДЕНДІ
«Ә. Б. БЕКТҰРОВ АТЫНДАҒЫ
ХИМИЯ ҒЫЛЫМДАРЫ ИНСТИТУТЫ»
АКЦИОНЕРЛІК ҚОҒАМЫ

ҚАЗАҚСТАННЫҢ ХИМИЯ ЖУРНАЛЫ

ХИМИЧЕСКИЙ ЖУРНАЛ КАЗАХСТАНА

CHEMICAL JOURNAL of KAZAKHSTAN

АКЦИОНЕРНОЕ ОБЩЕСТВО
ОРДЕНА ТРУДОВОГО КРАСНОГО ЗНАМЕНИ
«ИНСТИТУТ ХИМИЧЕСКИХ НАУК
им. А. Б. БЕКТУРОВА»

1 (61)

ЯНВАРЬ – МАРТ 2018 г.

ИЗДАЕТСЯ С ОКТЯБРЯ 2003 ГОДА

ВЫХОДИТ 4 РАЗА В ГОД

АЛМАТЫ
2018

UDC 547.652.1.304.2+543.429.23

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SYNTHESIS AND STRUCTURE OF 1,5-BIS(AMINOBUTYNILOXY)NAPHTHALINES

Abstract. New potentially biologically active 1,5-bis(aminobutynyloxy)naphthalenes were synthesized by the interaction of dipropynyloxynaphthalene with paraform and secondary amines under the catalysis of CuJ in dry dioxane at 45 °C.

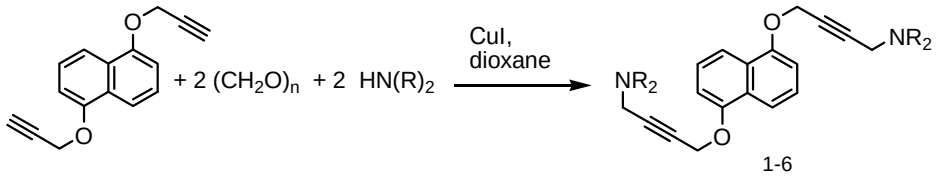
Keywords: Mannich reaction, 1,5-di(prop-2-ynyloxy)naphthalene, aminomethylation, 1,5-bis(aminobutynyloxy)naphthalenes, ^{1}H and ^{13}C NMR, PASS prediction.

The Mannich reaction, which takes place in the presence of copper monochloride in dioxane, is still one of the main methods of introducing an aminomethylene group to the neighboring position to a triple carbon-carbon bond. Authors of the article [1] give the results about the use of copper (II) acetate and ferric chloride (III) in aminomethylation reactions, the advantage of which is the use of ready-made salts of the corresponding metals in place of freshly-prepared copper monochloride. It is possible to use the Mannich reaction to prepare 2,6-diarylpiperidin-4-ones by a one-pot method by simultaneously reacting the ketone, benzaldehyde and amine component [2].

Previously, we investigated the reactivity of terminal acetylene hydrogen of 1,5-di(prop-2-ynyloxy)naphthalene in the aminomethylation reaction by some secondary amines under catalysis by copper monochloride [3] and copper monoiodide [4]. It was found that the use of copper monoiodide as a catalyst by heating of the reaction mixture to 45-50 °C in dry dioxane medium leads to less gum formation and allows reducing the reaction time to 3 hours.

In continuation of the di(prop-2-ynyloxy)naphthalenes terminal acetylene hydrogen reactivity investigation, we have now studied the aminomethylation of 1,5-di(prop-2-ynyloxy)naphthalene by diethylamine, dipropylamine, piperidine, morpholine, 3-morpholinopropane-1 -amine and methylpiperazine, shown in the figure 1 scheme.

The advantages of carrying out the reactions of aminomethylation under the catalysis by copper monoiodide include the increase of the reaction rate and the easy isolation of the products. Aminomethylated 1,5-bis(aminobutynyloxy) naphthalenes 1 – 6 are isolated by a simple treatment of the reaction mixture. After completion of the reaction, dioxane was distilled off, the precipitate was treated with ammonia (to remove copper iodide), extracted with benzene. The combined benzene extracts were dried by dry potassium. After distilling off the solvents, 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6 were obtained in the form



1 $NR_2 = N(CH_2CH_3)_2$; 2 $NR_2 = N(CH_2CH_2CH_3)_2$; 3 $NR_2 = N(CH_2)_5$; 4 $NR_2 = NCH_2CH_2OCH_2CH_2$;

5 $NR_2 = NH(CH_2)_3N(CH_2CH_2)_2O$; 6 $NR_2 = N(CH_2CH_2)_2NCH_3$;

Figure 1 – Scheme of 1,5-di(prop-2-ynyloxy)naphthalene aminomethylation

of oils. As a result, 4,4'-(naphthalene-1,5-diylbis(oxy))bis(N,N-diethylbut-2-yn-1-amine) 1 (in 65% yield), 4,4'- (naphthalene-1,5-diylbis(oxy))bis(N,N-dipropylbut-2-yn-1-amine) 2 (in 87% yield), 1,5-bis(4- (piperidin-1-yl)but-2-ynyloxy)naphthalene 3 (in 82% yield), 1,5-bis(4-morpholinobut-2-ynyloxy)naphthalene 4 (in 50% yield), 4.4'-(naphthalene-1.5-diylbis(oxy))bis(N-(3-morpholinopropyl)but-2-yn-1-amine) 5 (in 52% yield) and 1,5-bis(4-(4-methylpiperazin-1-yl) but-2-ynyloxy)naphthalene 6 (in 76% yield) were obtained.

The results of the reactions of aminomethylation show that 1,5-di(prop-2-ynyloxy)naphthalene is easily aminomethylated by the secondary diamines having various structure under copper monoiodide catalysis.

The structure of synthesized compounds 1 – 6 was proved on the basis of IR, ^1H, ^{13}C, COSY (^1H-^1H) and HMQC (^1H-^{13}C) spectroscopy data.

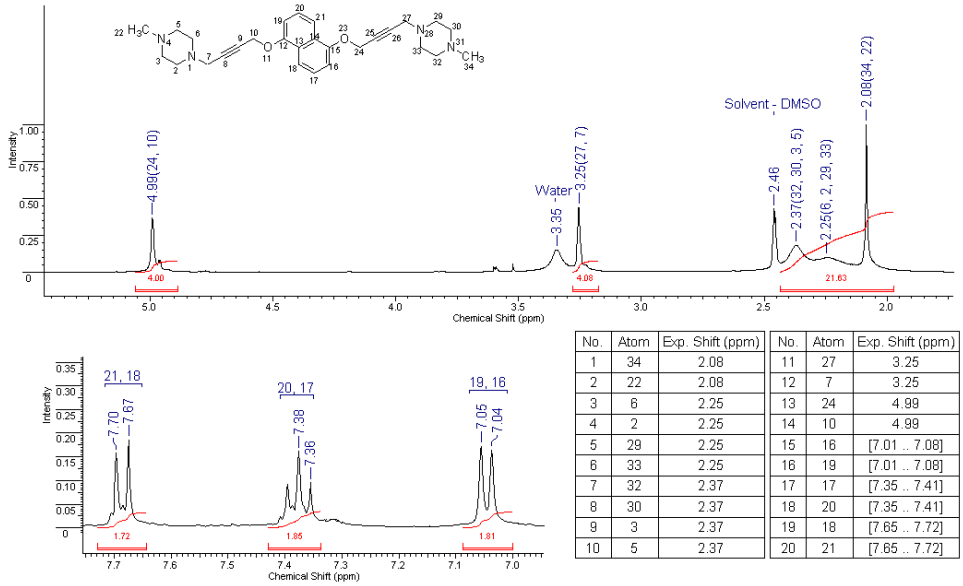
In the IR spectra of 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6, there is no absorption band in the 3300 cm^{-1} region, which is characteristic of the ≡CH terminal acetylenic group, but there is a weak band at 2118 cm^{-1}, which is characteristic for disubstituted C≡C bound, which confirms the aminomethylation reaction.

In the ^1H NMR spectra of 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6, the data of which are given in table 1, the new resonance signals appear in the corresponding regions characteristic for an aminomethylene group (in a range 3.25 – 3.37 ppm) and for the substituents at a nitrogen atom.

Table 1 – NMR ^1H (δ, ppm) NMR spectra of 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6

Comp.	Protons of naphthalene cycle			CH_2N	OCH_2	Protons of NR_2
	$H^{16}H^{19}$	$H^{17}H^{20}$	$H^{18}H^{21}$			$N(CH_2)_2$, $O(CH_2)_2$, CH_3
1	7,06	7,37	7,68	3,35	5,10	2,45; 0,94
2	7,06	7,34	7,67	3,32	4,91	2,46; 1,27; 0,71
3	6,98	7,34	7,88	3,27	4,85	2,49; 1,50; 1,54
4	6,90	7,30	8,07	3,27	4,89	2,71; 3,73
5	7,06	7,32	7,72	3,36	4,95	3,19; 3,54; 1,49
6	7,05	7,38	7,70	3,25	4,99	2,37; 2,25; 2,08
Note: The numbering of signals is given in accordance with figure 2.						

For example, in the ^{1}H NMR spectra of 1.5-bis(4-(4-methylpiperazin-1-yl)but-2-ynyloxy)naphthalene 6 shown in a figure 2, signals at 2.08, 2,25, and 2.37 ppm, are assigned to signals of symmetrical methylene groups of two methylpiperazine rings. Singlets at 4.99 ppm correspond to protons of O-methylene groups. Protons of aminomethyl substituents appear at 3.25 ppm in form of a broadened singlet. In the weak-field part of the spectrum, the signals of protons of the naphthalene nucleus are appeared, resonating in the region of 7.04-7.70 ppm.



No.	Atom	Exp. Shift (ppm)	No.	Atom	Exp. Shift (ppm)
1	34	2.08	11	27	3.25
2	22	2.08	12	7	3.25
3	6	2.25	13	24	4.99
4	2	2.25	14	10	4.99
5	29	2.25	15	16	[7.01 .. 7.08]
6	33	2.25	16	19	[7.01 .. 7.08]
7	32	2.37	17	17	[7.35 .. 7.41]
8	30	2.37	18	20	[7.35 .. 7.41]
9	3	2.37	19	18	[7.65 .. 7.72]
10	5	2.37	20	21	[7.65 .. 7.72]

Figure 2 – ^{1}H NMR spectrum of 1,5-bis(4-(4-methylpiperazin-1-yl)but-2-ynyloxy)naphthalene 6

In the ^{13}C NMR spectra of 1,5-bis(aminobutynyloxy)naphthalenes 1-6, the data of which are given in table 2, new resonance signals appear in the corresponding regions, characteristic for the aminomethylene group (in the range 42 – 50 ppm) and for the substituents of a nitrogen atom.

For example, in the carbon spectrum of 1,5-bis(4-(4-methylpiperazin-1-yl)but-2-ynyloxy)naphthalene 6, shown in figure 3, the most characteristic chemical shifts of carbon atoms –C≡C– 80.55 and 83.69 ppm. Signals of oxymethylene carbon atoms are manifested at 56.71 ppm. In the weak-field region at 107.27-153.16 ppm the signals of the carbon atoms of the naphthalene ring are located. Signals of CH_3N and CH_2N groups are appeared in the strong-field region at 46.22 and 46.71. The carbon atoms of the piperazine rings are resonated at 51.68 and 55.02 ppm.

The results of the interpretation of the two-dimensional spectrum in the HMQC (^{1}H-^{13}C) format, shown in figure 4, allow us to determine the correlation between chemical shifts of protons and chemical shifts of carbon nuclei, spin-spin interactions between nuclei, which allows us to establish the nature of heteronuclear interactions.

Table 2 – NMR ^{13}C (δ, ppm) NMR spectra of 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6

Соед.	OCH_2	–C≡C–	–C≡C–	$≡CCH_2$	NR_2
1	56,83	83,37	80,29	47,03	47,03; 12,93
2	56,47	85,3	81,05	42,02	55,47; 20,59; 12,21
3	53,30	79,80	75,60	47,90	56,70; 23,80; 25,80
4	56,84	79,7	78,01	47,08	52,22; 66,58
5	56,32	79,5	78,80	50,35	48,6; 24,53; 56,32; 53,80; 66,61
6	56,71	83,69	80,55	46,71	51,68; 55,02; 46,22
Соед.	Carbon atoms of the naphthalene ring				
	$C^{12}C^{15}$	$C^{16}C^{19}$	$C^{17}C^{20}$	$C^{18}C^{21}$	$C^{13}C^{14}$
1	153,18	107,48	125,81	114,7	126,73
2	153,44	107,70	126,17	115,93	127,54
3	153,30	106,40	125,10	115,30	126,80
4	153,01	107,6	126,77	114,88	128,99
5	152,96	107,04	125,83	114,64	128,69
6	153,16	107,27	126,52	114,68	128,85
Note: The numbering of signals is given in accordance with figure 3.					

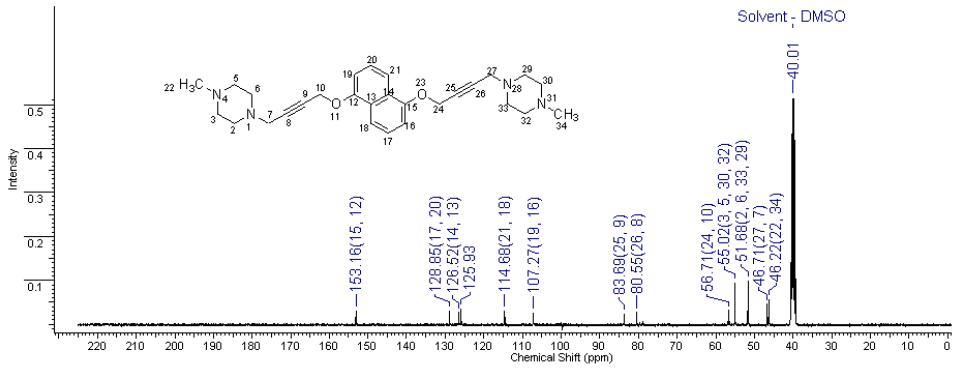


Figure 3 – ^{13}C NMR spectrum of 1,5-bis(4-(4-methylpiperazin-1-yl)-but-2-ynyloxy)naphthalene 6

The relationship "structure - biological activity" serves as a foundation for the purposeful creation of effective medicines. To determine the types of potential biological effects of synthesized compounds, a predictive assessment of the probable biological activity was carried out using the PASS (Prediction of Activity Spectra for Substance) computer program developed by the russian scientists V.V. Poroykov and D.A. Filimonov [5]. Using the computer program PASS - PharmaExpert, after analyzing the results of the forecast, it is possible to select those substances that are likely to possess the required set of activity types.

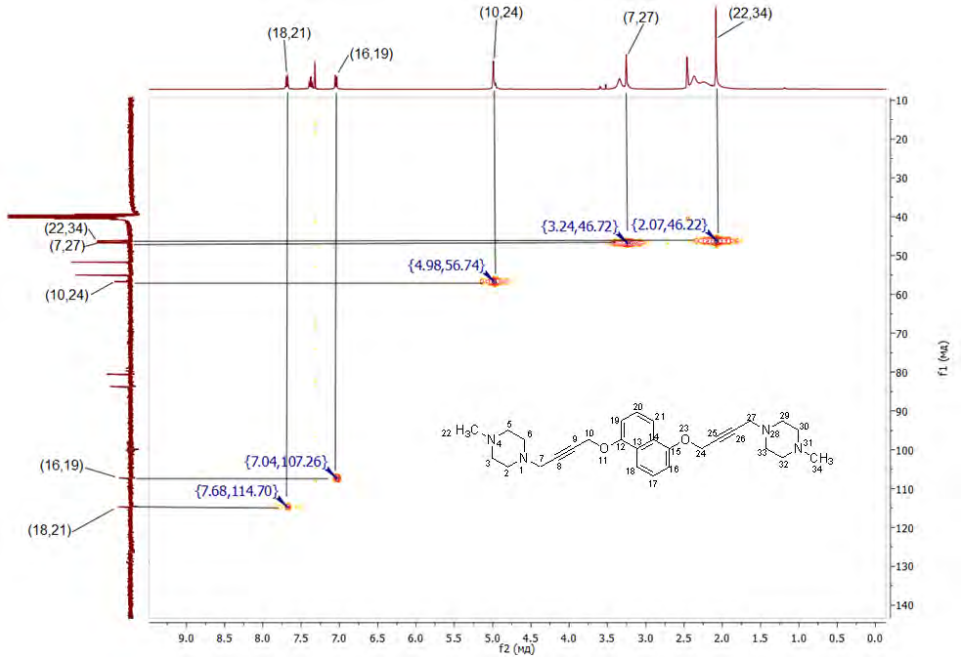


Figure 4 – Two-dimensional spectrum of 1,5-bis(4-(4-methylpiperazin-1-yl)but-2-ynyloxy) naphthalene 6 in the HMQC (^{1}H-^{13}C)

Analysis of data given in table 3 shows that 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6 potentially with a probability above 90% are the substrates of cytochrome CYP2C12 families (cytochromes are responsible for the metabolism of endogenous steroids of the body). For compounds 1, 2, 3, 5 with a probability from 60% to 93%, it is predicted spasmolytic activity in the treatment of bladder hyperactivity.

Table 3 – Predicted biological activity of 1,5-bis(aminobutynyloxy)naphthalenes 1 – 6

Chemical compounds	Probability of occurrence of predicted activity, %							
	CYP2C12 substrate	Spasmolytic, urinary	Anti-seborrheic	Anti-secretoric	Anti-neurotic	Phobic disorders treatment	Membrane integrity agonist	Anti-dyskinetic
1	94	93	86				76	70
2	91	89	78	70			82	
3	74	60		61	66	72	73	
4	68				75	87		
5		81			73	84		
6	67			59	75	69		

It should also be noted that for the 4,4'-(naphthalene-1,5-diylbis(oxy))-bis(N,N-diethylbut-2-yn-1-amine) 1 and 4,4'-(naphthalene-1,5-diylbis(oxy))-bis(N,N-dipropylbut-2-yn-1-amine) 2 the highest probability from 78% to 86% of the antiseborrheic activity in the treatment of children and adults seborrheic dermatitis (seborrhea). With the introduction of piperidine, morpholine, 3-morpholinopropane-1-amine and methylpiperazine, activity for the treatment of phobic disorders treatment (neuroses) (69-87%) and antineurotic activity (66-75%) is manifested. In addition, the compounds obtained revealed the possibility of manifesting antisecretoric and antidyskinetic activity.

Thus, as a result of the research work, new potential biological active 1,5-bis(aminobutynyloxy)naphthalenes have been synthesized. The structure of the synthesized compounds was established by the methods of IR spectroscopy, ^{1}H and ^{13}C NMR spectroscopy.

Experimental part

The course of the reaction and the purity of the products were monitored by thin-layer chromatography on "Silufol UV-254" plates, the eluent was a mixture of benzene and ethanol (1:3) with the appearance of substances spots with iodine vapor. The IR spectra are recorded on a Nicolet 5700 spectrometer in KBr tablets. The ^{1}H and ^{13}C NMR spectra of the samples were taken in DMSO-D_6 using a JNM-ECA 400 (Jeol) spectrometer with operating frequencies 400 (^{1}H), 100 MHz (^{13}C).

4,4'-(Naphthalene-1,5-diylbis(oxy))bis(N,N-diethylbut-2-yn-1-amine) 1. Solution of 0.3 g (0.0042 mol) diethylamine in dioxane 10 ml was dropped while stirring to a reaction mixture consisting of 0.5 g (0.0021 mol) of 1,5-di(prop-2-ynyloxy)naphthalene, 0.12 g (0.004 mol) of paraform, 0.12 g (0.0042 mol) of copper monoiodide in 20 ml of dioxane, and heated to 45 °C in a three-necked reaction flask equipped with a reflux condenser and a stirrer. After the end of the reaction, dioxane was distilled off. The residue was treated by aqueous ammonia solution and extracted by benzene. The extract was dried with potash, and the solvent was distilled off. The residue was applied to a column of silica gel, eluting by benzene. Chromatographically homogeneous fractions were combined, benzene was distilled off under reduced pressure. 4,4'-(Naphthalene-1,5-diylbis-(oxy))bis(N,N-diethylbut-2-yn-1-amine) 1 was obtained as an oil 0.56 g (65%).

4,4'-(Naphthalene-1,5-diylbis(oxy))bis(N,N-dipropylbut-2-yn-1-amine) 2. Similarly, from 0.5 g (0.0021 mol) of 1,5-di(prop-2-ynyloxy)naphthalene, 0.12 g of paraform, 0.43 g (0.0042 mol) of dipropylamine in the presence of 0.1 g of copper monoiodide in dioxane (at 45 °C) was obtained 0.85 g (87%) of diamine 2 as an oil.

1,5-Bis(4-(piperidin-1-yl)but-2-ynyloxy)naphthalene 3. Similarly, from 0.5 g (0.0021 mol) of 1,5-di(prop-2-ynyloxy)naphthalene, 0.12 g of paraform, 0.36 g (0.0042 mol) of piperidine in the presence of 0.1 g of copper monoiodide in dioxane (at 45 °C), 0.75 g (82%) of diamine 3 was obtained as an oil.

1,5-Bis(4-morpholinobut-2-ynyloxy)naphthalene 4. Similarly, from 0.4 g (0.0016 mol) of 1,5-di(prop-2-ynyloxy naphthalene, 0.12 g of paraform, 0.35 g (0.0032 mol) of morpholine in the presence of 0.1 g copper monoiodide in dioxane (at 45 °C), 0.37 g (50%) of diamine 4 was obtained as an oil.

4.4'-(Naphthalene-1.5-diylbis(oxy))bis(N-(3-morpholinopropyl)but-2-yn-1-amine) 5. Similarly, from 0.5 g (0.0021 mol) of 1,5-di(prop-2-ynyloxy)naphthalene, 0.12 g of paraform, 0.61 g (0.0042 mol) of morpholine in the presence of 0.1 g copper monoiodide in dioxane (at 45 °C) gave 0.58 g (53%) of diamine 5 as an oil.

1,5-Bis(4-(4-methylpiperazin-1-yl)but-2-ynyloxy)naphthalene 6. Similarly, from 0.5 g (0.0021 mol) of 1,5-di(prop-2-ynyloxy)naphthalene, 0.12 g of paraform, 0.42 g (0.0042 mol) of methyl piperazine in the presence of 0.1 g copper monoiodide in dioxane (at 45 °C), 0.74 g (76%) of diamine 6 was obtained as an oil.

The research was carried out according to the scientific and technical program No. BR05234667 within the framework of program-targeted financing CS MES RK.

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Резюме

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СИНТЕЗ И СТРОЕНИЕ
1,5-БИС(АМИНОБУТИНИЛОКСИ)НАФТАЛИНОВ

Новые потенциально биологически активные 1,5-бис(аминобутинилокси)нафталины синтезированы путем взаимодействия 1,5-дипропинилоксинафталина с параформом и вторичными аминами (диэтиламином, дипропиламином, морфолином, 3-морфолинопропаном, метилпиперазином) при катализе CuJ в среде сухого диок-

сана при температуре 45 °С с выходами от 50 до 87%. Сделана прогнозная оценка вероятной биологической активности по компьютерной программе PASS (Prediction of Activity Spectra for Substance).

Ключевые слова: 1,5-ди(проп-2-инилокси)нафталин, аминометилирование, 1,5-бис(аминобутинилокси)нафталины, ЯМР ^{1}Н и ^{13}С, PASS прогнозирование.

Резюме

Е. С. Сычева, Т. М. Сейілханов, С. А. Визер, Қ. Б. Ержанов

1,5-БИС(АМИНОБУТИНИЛОКСИ)НАФТАЛИНДЕРДІҢ СИНТЕЗІ ЖӘНЕ ҚҰРЫЛЫМДАРЫ

Жаңа потенциалды биологиялық белсенді 1,5-бис(аминобутинилокси)нафталиндер дипропинилоксинафталиннің параформмен және екіншілік аминдермен (диэтиламин, дипропиламин, морфолин, 3-морфолинопропан, метилпиперазин) CuJ катализі құрғақ диоксан ортасында 45 °С температурада әрекеттестіру жолы арқылы 50-ден 87 % дейінгі шығыммен синтезделген. PASS (Prediction of Activity Spectra for Substance) компьютерлік бағдарламасы бойынша ықтималды биологиялық белсенділікке болжаулар жүргізілді.

Түйін сөздер: 1,5-ди(проп-2-инилокси)нафталин, аминметилдеу, 1,5-бис(аминобутинилокси)нафталиндер, ЯМР ^{1}Н және ^{13}С, PASS бағдарлау.