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Selective and efficient Cu-catalyzed 1,3-bipolar cycloaddition of propargylthiobenzoxazoline and aryl azides

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Abstract

It was carried out selective synthesis of the 2-propargylthiobenzoxazoline. A cheap and convenient method for synthesis of new benzoxazole-triazole hybrid molecules were developed by carrying out 1,3-bipolar cycloaddition reactions of the obtained 2-propargylthiobenzoxazoline with some aromatic azides. Factors influencing the course and direction of the reaction (catalyst nature, ratio of reagents, reaction temperature and duration) have been identified. The IR-, 1H and 13C NMR spectra of the obtai Keywords: 2-propargylthiobenzoxazoline, arylazides, 1,3-bipolar cycloaddition, Cu (I) halides, hybrid molecules.ned substances were analyzed and it was proved that they correspond to their structures.

Keywords: Type your keywords here, separated by semicolons ;

1. Introduction

Currently, in the field of medicine and pharmaceuticals in the world, one of the urgent tasks is the search, selection and production of nonsteroidal low-toxic, synthetic, biologically active substances that can replace natural drugs. The main part of currently used synthetic and natural drugs with medicinal properties are heterocyclic compounds containing nitrogen, oxygen, and sulfur. Among them, there are many five-membered heterocyclic compounds with 3 nitrogen atoms - 1,2,3-triazoles.

Currently, one of the most important issues is the targeted synthesis of new, promising biologically active compounds, their successful use in agriculture and medicine against various diseases. In particular, benzoxazole derivatives include anti-inflammatory [1], analgesic [2], anticonvulsant [3] and antiviral [4], antimicrobial [5-8], against tuberculosis [9-13] and cancer [14, 15] drugs. Therefore, it is of particular importance to create cheap, highly effective and environmentally friendly local preparations, to improve their physico-chemical and biological properties.

There are several marketed drugs (Fig. 1) having benzoxazole as core active moiety like, *nonsteroidal anti-inflammatory drug* (*NSAID*) - flunoxaprofen, benoxaprofen, *antibiotic*—calcimycin, *antibacterial*—boxazomycin B, *muscle relaxant*—chloroxazone:

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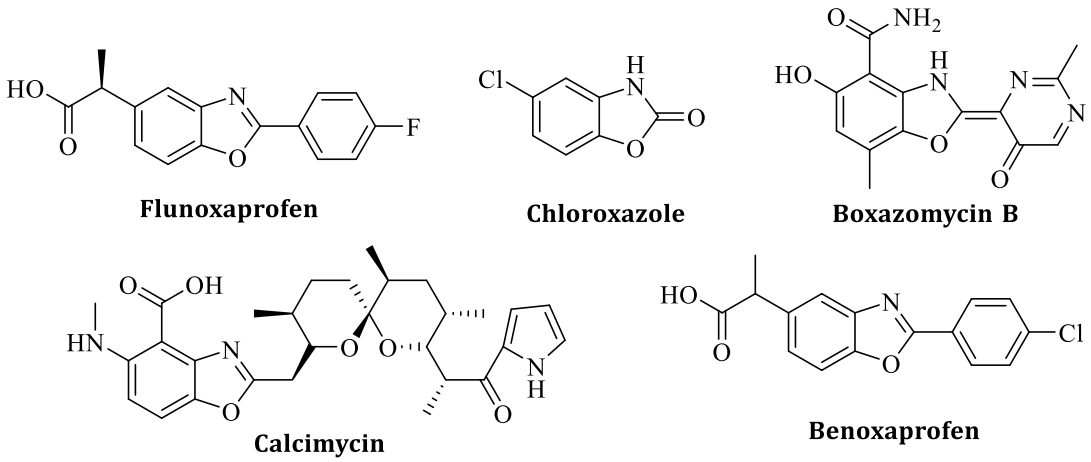


Figure 1. Marketed drugs containing benzoxazole core.

In Fig.2 are shown marketed drugs and biologically active molecules containing 1,2,3-triazoles, which possess antifungal, antibiotic, anticancer and anti-HIV activities.

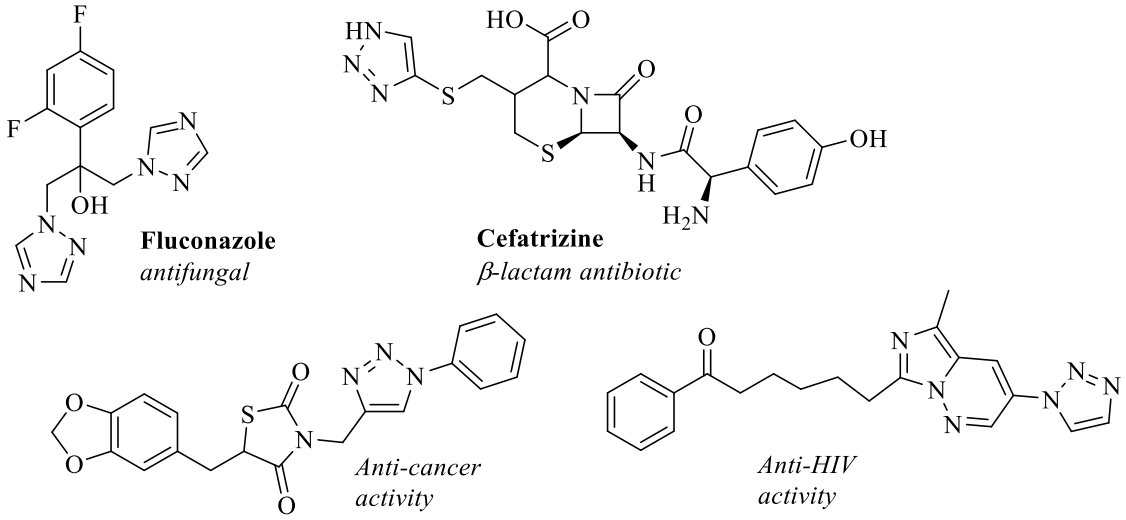


Figure 2. Marketed drugs and bioactive molecules containing 1,2,3-triazole core.

Although research in the field of benzoxazoles and their analogues - benzimidazoles and benzothiazoles began long ago, scientific and practical research based on compounds of this class is being conducted intensively in many countries of the world [16-18].

2. Experimental

IR spectra were recorded on a System 2000 IR Fourier spectrometer in KBr tablets, 1H NMR spectra - on a Unity-400+ instrument (operating frequency 400 MHz, internal standard TMS, δ scale) solvents - CD3OD, DMSO-d6. The purity of the products and the progress of the reaction were monitored by TLC on Silufol UV-254 in the system - benzene: methanol - 5:1. The melting points of the synthesized compounds were determined on the "Mel-temp" (Germany) device.

Synthesis of 2-propargylthiobenzoxazoline (2) was carried out according to the method described in the literature [7]. From 7.5 g (0.05 mol) of benzoxazole-2-thiol (**1**), 5 ml (7.85 g, 0.066 mol, d=1.57 g/mol) of propargyl bromide, 5 g (0.036 mmol) of potash and 80 ml of acetone according to the

method 7.05 g (75%) of product (**2**) was obtained, melting point 48-50ºC, R_f 0.44 (benzene:methanol – 5:1).

2-(((1-(3-Nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-benzo[d]oxazole (3). (***General procedure***).

0.378 g (2 mmol) of 2-propargylthiobenzoxazoline (**2**), 0.328 g (2 mmol) of *meta*-nitrophenylazide, 0.008 g (0.021 mmol) of copper(I) iodide and 30 ml of toluene were placed into a round-bottom flask. The flask placed on a hot plate and connected to a reflux condenser, and a mixture was heated at the boiling point of toluene (110ºC) for 5 hours. The progress of the reaction was monitored by thin layer chromatography. After the end of the reaction, a yellow precipitate began to form in the reaction mixture. The mixture was left overnight at room temperature, the formed precipitates filtered off, dried and 0.616 g (87.5%) product (**3**) was obtained, melting point 140-142^{0}C, R_f 0.58 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.99 (1H, s, Het-H), 7.74 (3H, m, H-4,2`,6`), 7.29 (5H, m, H-5,6,7,3`,5`), 4.70 (2H, s, $\underline{CH_2}$-S). ^{13}C NMR (100 MHz, DMSO-d6+CCl_4, δ, ppm): 163.93 (C-2), 152.13 (C-7^a), 149.03 (C-3^a), 144.29 (C-3`), 142.03 (C-6`), 137.92 (C-4, triazole ring), 131.55 (C-1`), 128.24 (C-5`), 124.59 (C-5), 124.01 (C-6), 123.11 (C-4`), 122.69 (C-4), 118.76 (C-5, triazole ring), 115.18 (C-7), 110.28 (C-2`), 26.86 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3688 (C–H aryl), 2960 (CH_2 group), 1288 (C–N), 781 (C–S-C), 756 (NO_2).

2-(((1-(4-Nitro)-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]oxazole (4).

Yield 0.619 g (80.5%), melting point 118-120^{0}C, R_f 0.61 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.94 (1H, s, Het-H), 8.36 (2H, d, J=9.2, H-3`,5`), 8.20 (2H, d, J=9.35, H-2`, 6`), 7.57 (1H, m, H-7), 7.47 (1H, dd, J_1=1.49, J_2=7.08, H-4), 7.24 (2H, m, H-5,6), 4.70 (2H, s, $\underline{CH_2}$-S). ^{13}C NMR (100 MHz, DMSO-d6+CCl_4, δ, ppm): 163.90 (C-2), 152.13 (C-7^a), 147.03 (C-4`), 144.47 (C-1`), 142.31 (C-3^a), 141.40 (C-4, triazole ring), 125.63 (C-5), 124.58 (C-6), 124.23 (C-3`, C-5`), 122.65 (C-2`, C-6`), 120.81 (C-5, triazole ring), 118.77 (C-4), 110.27 (C-7), 26.80 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3094 (Ar(=C-H)), 749 (C-S-C group), 1597 (N=N), 1342 (=C-H), 1455 (C-O), 1236 (C-N), , 749 (NO_2), 682 (Ar (=C-H) deformation vibration).

4-(4-((Benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (5).

Yield 0.619 g (88%), melting point 263-265^{0}C, R_f 0.68 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.78 (1H, s, Het-H), 8.08 (2H, d, J=8.83, H-3`,5`), 7.95 (2H, d, J=8.96, H-2`, 6`), 7.57 (1H, m, H-7), 7.47 (1H, dd, J_1=1,45, J_2=7.02, H-4), 7.24 (2H, m, H-5, 6), 4.69 (2H, s, $\underline{CH_2}$-S). ^{13}C NMR (100 MHz, DMSO-d6+CCl_4, δ, ppm): 166.65 (C-COOH), 164.04 (C-2), 152.13 (C-7^a), 143.94 (C-1`), 142.03 (C-3$^a$), 139.93 (C-4, triazole ring), 131.41 (C-3`, 5`), 131.27 (C-4`), 124.57 (C-5), 124.2 (C-6), 122.21 (C-2`, C-6`), 119.80 (C-5, triazole ring), 118.74 (C-4), 110.26 (C-7), 26.89 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3059 (Ar(=C-H)), 1678 (C=C), 1558 (N=N), 1455 (=C-H), 1430, 1241 (C-N), 685 (Ar (=C-H) deformation vibration)

2-(((1-(2-Bromo-4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-benzo[d]oxazole (6).

Yield 0.59 g (68%), melting point 144-145ºC, R_f 0.69 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, $CDCl_3$ +CCl_4, δ, ppm, *J*/Hz): 8.59 (1H, d, J=2.67, H-3`), 8.32 (2H, m, Het-H, H-5`), 7.80 (1H, d, J=8.70, H-6`), 7.60 (1H, m, H-7), 7.44 (1H, m, H-4), 7.28 (2H, m, H-5,6), 4.70 (2H, s, $\underline{CH_2}$-S). $^{13}$C NMR (100 MHz, DMSO-d6+$CCl_4$, δ, ppm): 164.06 (C-2), 152.20 (C-7$^a$), 148.18 (C-4`), 144.18 (C-3^a), 141.81 (C-1`), 141.14 (C-4, triazole ring), 129.54 (C-6`), 128.69 (C-3`), 125.05 (C-5), 124.58 (C-6), 124.34 (C-5`), 123.71 (C-2`), 118.50 (C-5, triazole ring), 118.18 (C-4), 110.26 (C-7), 26.89 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3079 (Ar(=C-H)), 750 (C-S-C group), 1621 (C=C), 1454 (N=N), 1238 (C-N), 758 (NO_2), 664 (Ar (=C-H) deformation vibration).

2-(((1-(2-Methyl-4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methyl)thio)benzo[d]oxazole (7).

Yield 0.28 g (82%), melting point 145-146^{0}C, Rf 0.55 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.47 (1H, s, Het-H), 8.24 (1H, d, J=1.67, H-5`), 8.03 (1H, s, H-3`), 7.67 (1H, m, H-6`), 7.56 (1H, m, H-7), 7.47 (1H, m, H-4), 7.24 (2H, m, H-5,6), 4.70 (2H, s, $\underline{CH_2}$-S), 2.31 (3H, s, Ar-$\underline{CH_3}$). $^{13}$C NMR (100 MHz, DMSO-d6+$CCl_4$, δ, ppm): $^{13}$C NMR (100 MHz, DMSO-d6+$CCl_4$, δ, ppm): 164.09 (C-2), 152.12 (C-7$^a$), 146.61 (C-4`), 143.19 (C-3^a), 142.01 (C-2`), 141.39 (C-1`), 137.06 (C-4, triazole ring), 133.10 (C-6`), 125.79 (C-3`), 124.56 (C-5), 124.31 (C-6), 124.21 (C-5`), 123.71 (C-2`),

1121.30 (C-5, triazole ring), 118.70 (C-4), 110.27 (C-7), 26.80 (CH_2). 18.79 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3083 (Ar(=C-H)), 739 (C-S-C group), 1647 (C=C), 1597 (N=N), 1452 (=C-H), 1407 (C-O), 1233 (C-N), 880 (NO_2).

2-(((1-(3,4-Dichlorophenyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-benzo[d]oxazole (8).

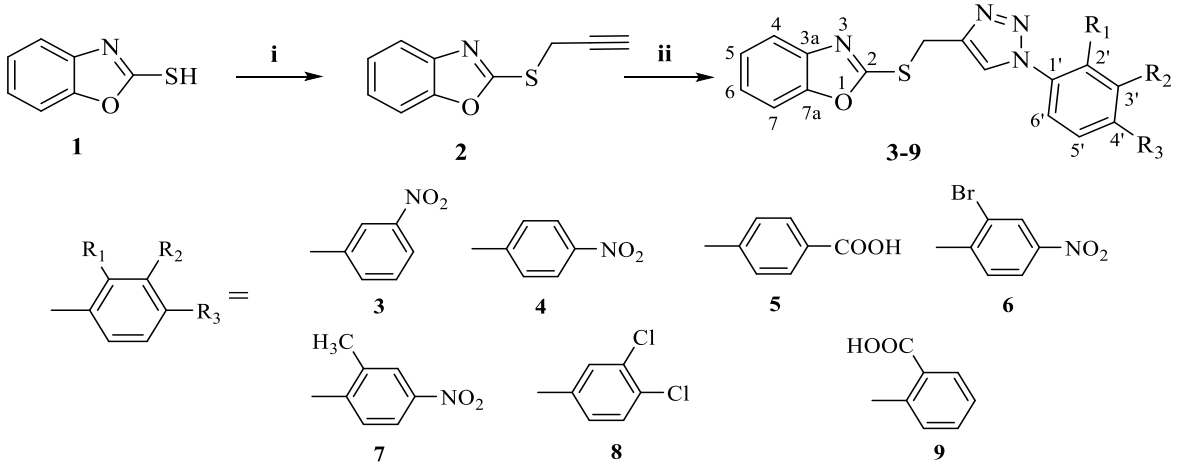
Yield 0.288 g (76.5%), melting point 138-140^{0}C, Rf 0.44 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.80 (1H, s, Het-H), 7.23 (2H, m, H-5, 6), 7.47 (1H, dd, J_1=2.01, J_2=7.47, H-4), 7.57 (1H, dd, J_1=1.30, J_2=6.50, H-7), 8.14 (1H, d, J=2.61, H-2`), 7.88 (1H, dd, $J_1$=2.53, $J_2$=8.77, H-6`), 7.65 (1H, d, J=8.70, H-5`), 4.67 (2H, s, $CH_2$-S). $^{13}$C NMR (100 MHz, DMSO-d6+$CCl_4$, δ, ppm): 163.95 (C-2), 152.12 (C-7$^a$), 144.09 (C-3$^a$), 142.01 (C-1`), 136.52 (C-4`), 133.24 (C-3`), 131.79 (C-4, triazole ring), 124.58 (C-5`), 124.22 (C-5), 122.38 (C-6), 122.10 (C-6`), 120.03 (C-5, triazole ring), 118.76 (C-4), 110.28 (C-7), 26.86 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3081 (Ar(=C-H)), 748 (C-S-C group), 1623 (C=C), 1458 (N=N), 1236 (C-N), 665 (Ar (=C-H) deformation vibration).

2-(4-((Benzo[d]oxazol-2-ylthio)methyl)-1H-1,2,3-triazol-1-yl)benzoic acid (9).

Yield 0.58 g (82%), melting point 158-160^{0}C, R_f 0.57 (benzene:methanol – 5:1). ^{1}H NMR (400 MHz, DMSO-d6+CCl_4, δ, ppm, *J*/Hz): 8.24 (1H, s, Het-H), 7.91 (1H, dd, J_1=1.56, J_2=7.67, H-6`), 7.64 (1H, td, $J_1$=1.75, $J_2$=7.60, H-4`), 7.57 (2H, m, H-3`, 5`), 7.47 (2H, m, H-4, 7), 7.24 (2H, m, H-5, 6), 4.70 (2H, s, CH_2-S). ^{13}C NMR (100 MHz, DMSO-d6+CCl_4, δ, ppm): 166.56 (C-COOH) 164.28 (C-2), 152.10 (C-7^a), 142.44 (C-3^a), 142.03 (C-5`), 136.05 (C-4, triazole ring), 132.33 (C-2`), 131.08 (C-3`), 129.83 (C-1`), 129.07 (C-6`), 126.82 (C-4`), 125.47 (C-5), 124.55 (C-6), 124.16 (C-5, triazole ring), 118.71 (C-4), 110.25 (C-7), 26.96 (CH_2). IR-spectrum (KBr, ν, cm^{-1}): 3142 (Ar(=C-H)), 1602 (C=C), 1583 (N=N), 1452 (=C-H), 1237 (C-N), 693 (Ar (=C-H) deformation vibration).

3. Results and discussion

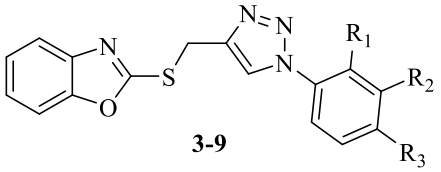
We carried out cycloaddition reactions in the presence of copper (I) iodide and copper (I) bomide. Only one triazole isomer was found to form from the reaction. The reaction was carried out by heating a 1:1 mixture of 2-propargylthiobenzoxazoline and various substituted aromatic azides in the presence of a small amount of copper(I) iodide and copper(1) bromide as catalyst in a toluene solution at a temperature of 110^{o}C for 5 hours:



i) 1:Propargyl bromide:K_2CO_3 - 1:1.32:0.72, acetone, 56^{o}C, 5 h;
ii) 2:Arylazide:Cu_2I_2 (Cu_2Br_2) - 1:1:2.1 10^{-8}, toluene, 110^{o}C, 5 h.

The progress of the reaction was monitored by thin layer chromatography. A benzene:methanol (5:1) system was used as an eluent. As a result, the corresponding 1,4-disubstituted triazole derivatives (**3-9**) were isolated in high yields (68-88%).

Table 1. Some physico-chemical data of the obtained hybrid molecules (**3-9**).



3-9

№	Compound	R_1	R_2	R_3	Brutto formula	Rf*	Melting point, ^0C	Yield, %
1	**3**	H	NO_2	H	$C_{16}H_{10}N_5SO_3$	0.58	140-142	87,5
2	**4**	H	H	NO_2	$C_{16}H_{10}N_5SO_3$	0.61	118-120	80,5
3	**5**	H	H	COOH	$C_{17}H_{11}N_4SO_3$	0.68	263-265	81.5
4	**6**	Br	H	NO_2	$C_{16}H_9N_5SBrO_3$	0.69	144-145	68
5	**7**	CH_3	H	NO_2	$C_{17}H_{12}SO_3N_5$	0.55	145-146	82
6	**8**	H	Cl	Cl	$C_{16}H_9SN_4OCI_2$	0.44	138-140	76.5
7	**9**	COOH	H	H	$C_{17}H_{11}N_4SO_3$	0.57	158-160	82

*System: benzene: methanol - 5:1.

We have chosen the method of obtaining solvent toluene, catalyst copper (I) iodide and copper (I) bromide as optimal conditions. By this method, the reaction was carried out at the boiling temperature of toluene for 5 hours. As a result, the corresponding 1,4-substituted triazole derivatives (**3-6**) were isolated in high yields (68-87.5%). The cyclization of 2-propargylthiobenzoxazoline with *meta*-nitrophenylazide showed the highest reaction yield of 87.5% (after recrystallization).

Table 2. The multiplicity of the corresponding protons (δ, ppm) in the ^1H NMR-spectrum of the obtained compounds (**3-9**)

№	S-C<u>H</u>$_2$	Ar-H	Het-H	Other groups
3	4.70 (2H, s)	7.74 (3H, m, H-4,2`,6`), 7.29 (5H, m, H-5,6,7,3`,5`)	8.99 (1H, s)	
4	4.70 (2H, s)	8.36 (2H, d, J=9.2, H-3`,5`), 8.20 (2H, d, J=9.35, H-2`,6`), 7.57 (1H, m, H-7), 7.47 (1H, dd, J_1=1.49, J_2=7.08, H-4), 7.24 (2H, m, H-5,6)	8.94 (1H, s)	
5	4.69 (2H, s)	8.08 (2H, d, J=8.83, H-3`,5`), 7.95 (2H, d, J=8.96, H-2`, 6`), 7.57 (1H, m, H-7), 7.47 (1H, dd, J_1=1,45, J_2=7.02, H-4), 7.24 (2H, m, H-5, 6)	8.78 (1H, s)	
6	4.70 (2H, s)	8.59 (1H, d, J=2.67, H-3`), 8.32 (2H, m, Het-H, H-5`), 7.80 (1H, d, J=8.70, H-6`), 7.60 (1H, m, H-7), 7.44 (1H, m, H-4), 7.28 (2H, m, H-5,6), 4.70 (2H, s, <u>CH$_2$</u>-S)	8.32 (2H, m, Het-H, H-5`)	
7	4.70 (2H, s)	8.24 (1H, d, J=1.67, H-5`), 8.03 (1H, s, H-3`), 7.67 (1H, m, H-6`), 7.56 (1H, m, H-7), 7.47 (1H, m, H-4), 7.24 (2H, m, H-5,6)	8.47 (1H, s)	2.31 (3H, s, Ar-<u>CH$_3$</u>)
8	4.67 (2H, s)	7.23 (2H, m, H-5, 6), 7.47 (1H, dd, J_1=2.01, J_2=7.47, H-4), 7.57 (1H, dd, J_1=1.30, J_2=6.50, H-7), 8.14 (1H, d, J=2.61, H-2`), 7.88 (1H, dd, $J_1$=2.53, $J_2$=8.77, H-6`), 7.65 (1H, d, J=8.70, H-5`)	8.80 (1H, s)	
9	4.70 (2H, s)	7.91 (1H, dd, J_1=1.56, J_2=7.67, H-6`), 7.64 (1H, td, $J_1$=1.75, $J_2$=7.60, H-4`), 7.57 (2H, m, H-3`, 5`), 7.47 (2H, m, H-4, 7), 7.24 (2H, m, H-5, 6)	8.24 (1H, s)	

Structure of the resulting triazole derivatives confirmed by IR, ^{1}H and ^{13}C NMR spectra. In ^{1}H NMR spectrum (DMSO-d6+CCl_4) of 2-(((1-(4-nitro)-1H-1,2,3-triazol-4-yl)methyl)thio)-benzo[d]oxazole (**4**), protons of the methylene group connecting the triazole ring are in a relatively weak area – at 4.70 ppm as two-protonic singlet (2H, s, S-CH_2). Protons of the benzoxazole ring of molecule are: an one-protonic multiplet at 7.57 ppm (1H, m, H-7), one-protonic dublet of dublets at 7.47 (1H, dd, J_1=1.49, J_2=7.08, H-4), and two-protonic multiplet at 7.24 ppm (2H, m, H-5,6), signals of protons of 4-nitrophenyl group are found at 8.36 ppm (2H, d, J=9.2, H-3`,5`) and 8.20 ppm (2H, d, J=9.35, H-2`,6`). The proton in the triazole ring (Het-H) has a chemical shift as one-protonic singlet in a rather weak field - 8.94 ppm (1H, s).

4. Conclusions

Thus, as a result of the conducted research, new benzoxazole-triazole hybrid molecules **3-9** were synthesized on the basis of *Cu*-catalyzed 1,3-bipolar cycloaddition reactions, which are very important for synthetic organic chemistry. These substances are targeted synthesis products. The structure of the synthesized compounds was proved using modern physical research methods: IR- and ^{1}H NMR-spectroscopy. The conducted researches are important for the determination of the alternative synthesis, structure and reactivity of tricyclic 2-mercaptobenzoxazole and their new derivatives, as well as for the creation of new biologically active substances.

5. Conflicts of interest

There are no conflicts to declare.

6. Acknowledgment

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