

SYNTHESIS, PHYSICAL and chemical PROPERTIES of SOME Derivatives 1,2,4-triazolo-(3,4-b)-1,3,4-THIODIAZINE WITH RESIDUE OF FRAGMENTS OF FURAN

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KEYWORDS: synthesis of new 1,2,4-triazolo-(3,4-b)-1,3,4-thiodiazines, research of physical and chemical properties.

INTRODUCTION. The state of modern medical, pharmaceutical, veterinary industry needs introduction of new low-toxic and effective medications with the wide spectrum of pharmacological action. Among bioactive matters into first place synthetic derivatives go out in this search [1-5, 12].

The famous methods of synthesis of 1,2,4-triazolo-[3,4-b] -[1,3,4]-thiodiazines [7, 10] are based mainly on formation of C-N,C-S connections on the final stage of heterocyclization at co-operating of initial 4-amino-3-thio-1,2,4-triazoles with bifunctional reagents. Unlike the derivatives of N-amino-2-thioimidazoles, the polycyclic systems on the basis of aminothiotriazoles are studied not so widely. It is known that the derivatives of aminothiotriazoles show the wide spectrum of anti-virus activity, in particular are the inhibitors of replication of virus of man immunodeficiency (HIV) [3, 10].

Scientific achievements of pharmaceutical science of the last years testify to wide perspective possibilities of synthetic constituent in this industry. Synthesis of biologically active connections is a basis of creation of potential remedies. There are a lot of synthetic directions of pharmacological active matters search[1-3]. The key aspect of search is a creation of low-toxic substances with the wide spectrum of biological action. Analyzing literary sources it follows notices, that large synthetic possibilities find out the heterocyclic systems [7]among which priority are derivatives of 1,2,4-triazole. It is known also [8-12], that connections of this class are

low-toxic or practically un toxic matters which find out the different types of pharmacological activity. Combination in one molecule of structural fragments of 1,2,4-triazole, aliphatic, aromatic [14] or heterocyclic systems results in appearance of new molecules with high biological activity.

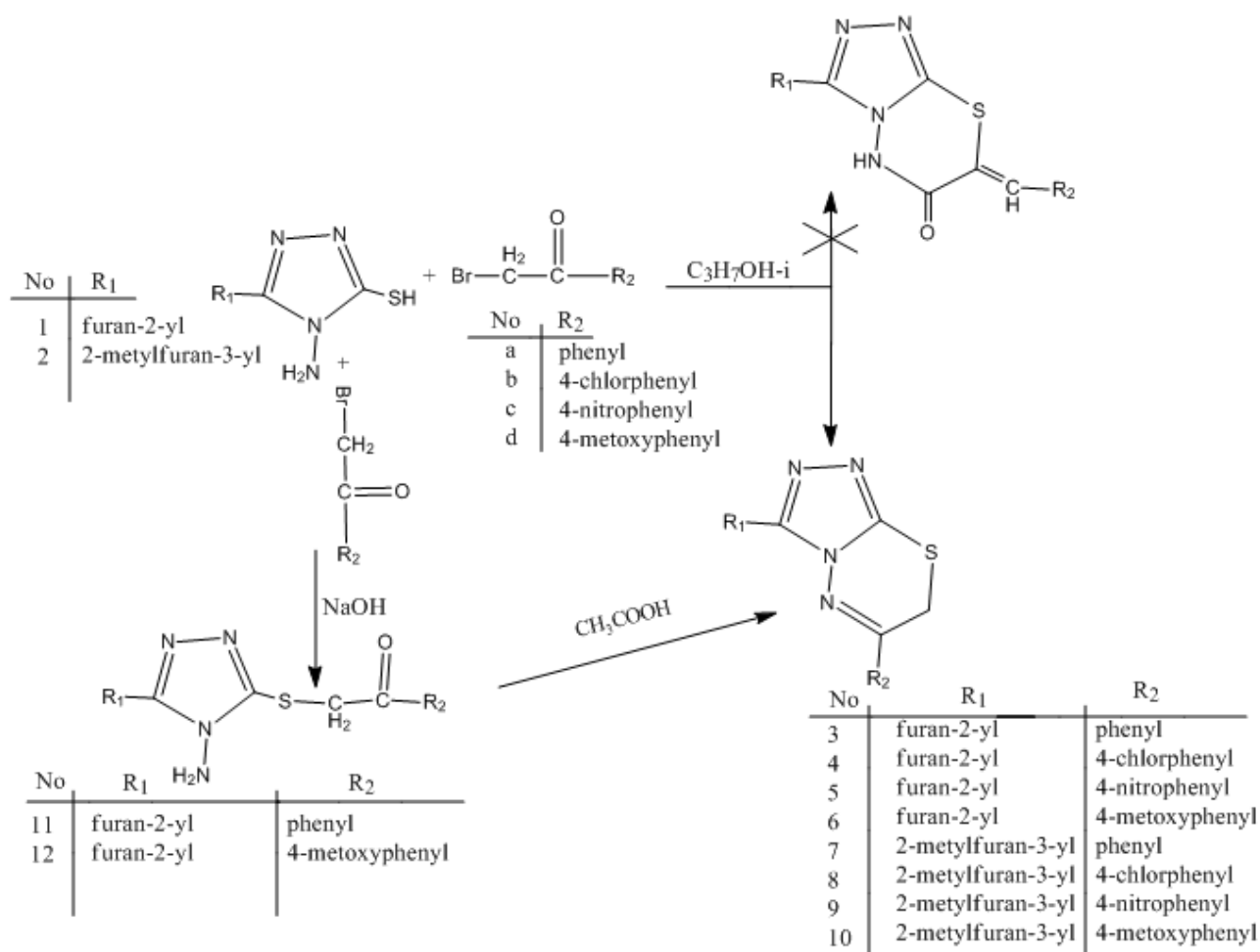
Before marked [15] by us, that introduction to the nucleus of 1,2,4-triazole according to the fifth regulations of fragments of furan and on the fourth of some aliphatic and aromatic systems causes the increase of pharmacological action [4], and sometimes to the display of new activity [5, 6].

PURPOSE OF WORK. Continuing scientific researches, we synthesized the new condensed systems on the basis of nucleus of 1,2,4-triazole with residues of fragments of furan (scheme 1).

RESEARCH METHODS. The synthesis of the proper structures (scheme 1) is carried out by us by two methods. The first method foresees co-operation of 5-(furan-2-yl)-4-amino-1,2,3-triazole-3-thiol (1) and 5-(2-methylfuran-3-yl)-4-amino-1,2,4-triazole-3-thiol (2) with the equivalent amount of proper 2-bromine-1-aryletanone (a-d) in the environment of i-propanole. In theory a similar reaction can pass with formation of different derivatives (scheme 1). Products can be 3-(furan-2-yl, 2-methylfuran-3-yl)-6-aryl-7H[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiodiazine or derivatives of 1,2,4-triazolo-[3,4-b]-[1,3,4]-thiodiazine-6(7H)-one.

Also to our opinion interest caused the second method is a reaction of cyclization of 2-[5-(furfurane-2-yl)-4-amino-1,2,4-triazole-3-ylthio]-1-aryletanones (11, 12, scheme 1). In theory the products of this reaction can be proper to thiodiazines (scheme1), as potential pharmacological active matters [13]. A reaction was conducted in the environment of acetate acid during the eight hours boiling. Connections which got after two methods do not give depression of melting temperature which show by itself white (3, 4, 6-8, 10-12, tabl. 1), yellow (5, 9, tabl. 1) crystalline matters which are hardly soluble in water and organic solvents. For an

analysis matters are recrystallized from an ethanol (3-6, 11, 12, tabl. 1) or i-propanole (7-10, tabl. 1).



Scheme 1

Synthesis of 3-(furan-2-yl, 2-methylfuran-3-yl)-6-aryl-7H-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thidiazines

RESULTS AND THEIR DISCUSSIONS. Therefore the row of connections the structure of which is confirmed by complex physical and chemical methods (element analysis, UV-, IR-spectroscopy, PMR-, mass-spectrometry, in some cases X-ray-structred analysis is applied) and their individuality is taken chromatographically.

So in the IR-spectra of 3-(furan-2-yl, 2-methylfuran-3-yl)-6-aryl-7H-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thidiazines stripes of absorption of carbonic group are absent, which confirms passing of reaction of cyclization, presence stripes of

absorption of nucleus of furan, and also stripes of absorption of aromatic ring (table 2).

Table 1. Yields, Melting points, Formulas and Elemental Analysis for Compounds

Comp d.	R ₁	R ₂	Yield (%)	M.p.°C	Formula	Found (required) (%)			
						C	H	N	S
3	Furan-2-yl	Ph	54	161	C ₁₄ H ₁₀ N ₄ OS	59.47(59.56)	3.56(3.57)	19.83(19.85)	11.34(11.36)
4	Furan-2-yl	4-ClPh	61	185	C ₁₄ H ₉ ClN ₄ OS	53.02(53.08)	2.85(2.86)	17.66(17.69)	10.09(10.12)
5	Furan-2-yl	4-NO ₂ Ph	69	201	C ₁₄ H ₉ N ₅ O ₃ S	51.29(51.37)	2.77(2.77)	21.42(21.40)	9.77(9.80)
6	Furan-2-yl	4-OCH ₃ Ph	55	172	C ₁₅ H ₁₂ N ₄ O ₂ S	57.54(57.68)	3.85(3.87)	17.92(17.94)	10.25(10.27)
7	2-Metylfuran-3-yl	Ph	57	144	C ₁₅ H ₁₂ N ₄ OS	60.69(60.74)	4.06(4.08)	18.87(18.91)	10.79(10.82)
8	2-Metylfuran-3-yl	4-ClPh	60	160	C ₁₅ H ₁₁ ClN ₄ OS	54.38(54.46)	3.33(3.35)	16.91(16.94)	9.67(9.69)
9	2-Metylfuran-3-yl	4-NO ₂ Ph	73	181	C ₁₅ H ₁₁ N ₅ O ₃ S	52.69(52.78)	3.23(3.25)	20.49(20.52)	9.36(9.39)
10	2-Metylfuran-3-yl	4-OCH ₃ Ph	87	230	C ₁₆ H ₁₄ N ₄ O ₂ S	58.82(58.88)	4.29(4.32)	17.15(17.17)	9.78(9.82)
11	Furan-2-yl	Ph	90	146	C ₁₄ H ₁₂ N ₄ O ₂ S	55.87(55.99)	4.01(4.03)	18.61(18.65)	10.66(10.68)
12	Furan-2-yl	4-OCH ₃ Ph	75	166	C ₁₅ H ₁₄ N ₄ O ₃ S	54.49(54.53)	4.25(4.27)	16.95(16.96)	9.69(9.71)

Table 2. Infra red (KBr, cm⁻¹) Spectral Data for Compounds.

No	C=O	C=N	CH ₂	NH	No	C=O	C=N	CH ₂	NH
3	-	1490	1240	-	8	-	1510	1180	-
4	-	1495	1250	-	9	-	1495	1230	-
5	-	1510	1215	-	10	-	1480	1170	-
6	-	1500	1190	-	11	1715	1485	1195	3340
7	-	1505	1205	-	12	1705	1505	1210	3325

In addition PMR - spectra of 3-(furan-2-yl, 2-methylfuran-3-yl)-6-aryl-7H-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiodiazines are investigated (table 3). The presence of clear signals of protons (4.42 m.h.) testifies to the presence of methylene fragments, and absence of signals of protons of aminogroup (5.77 m.h.) leads to the passing of reaction of cyclization. Also there are signals of protons of aromatic ring (7.06m.h., 7.91 m.h.) and nucleus of furan (7.58 m.h., 6.42m.h.).

Table 3. ¹H-NMR Spectral Data for Compounds.

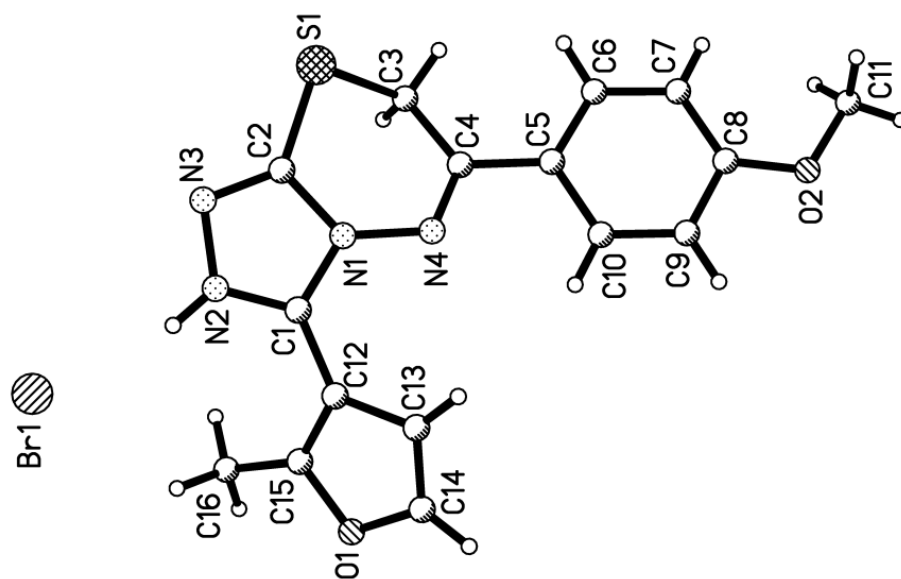
No	¹ H-NMR (DMSO-d ⁶ δ ppm)
3	8.15(d, 1H, Fur-H), 7.93(t, 2H, Ar-H), 7.51(q, 3H, Ar-H), 7.20(d, 1H, Fur-H), 6.66(t, 1H, Fur-H), 4.41(s, 2H, CH ₂)
4	8.13(d, 1H, Fur-H), 7.97(d, 2H, Ar-H), 7.51(d, 2H, Ar-H), 6.67(t, 1H, Fur-H), 4.42 (s, 2H, CH ₂)
5	8.32(d, 2H, Ar-H), 8.08(d, 2H, Ar-H), 8.13(d, 1H, Fur-H), 7.20(d, 1H, Fur-H), 6.67(t, 1H, Fur-H), 4.41(s, 2H, CH ₂)
6	8.14(d, 1H, Fur-H), 7.90(d, 2H, Ar-H), 7.05(d, 2H, Ar-H), 7.20(d, 1H, Fur-H), 6.67(t, 1H, Fur-H), 3.82(s, 3H, OCH ₃), 4.42(s, 2H, CH ₂)
7	7.93(t, 2H, Ar-H), 7.51(m, 3H, Ar-H), 6.41(d, 1H, Fur-H), 2.29(s, 3H, FurCH ₃), 4.42(s, 2H, CH ₂)
8	7.97(d, 2H, Ar-H), 7.51(d, 2H, Ar-H), 6.42(d, 1H, Fur-H), 4.42(s, 2H, CH ₂), 2.29(s, 3H, FurCH ₃)
9	8.32(d, 2H, Ar-H), 8.08(d, 2H, Ar-H), 7.57(d, 1H, Fur-H), 6.41(d, 1H, Fur-H), 4.42(s, 2H, CH ₂), 2.31(s, 3H, FurCH ₃)
10	7.91(d, 2H, Ar-H), 7.58(d, 1H, Fur-H), 7.06(d, 2H, Ar-H), 4.42(s, 2H, CH ₂), 3.83(s, 3H, OCH ₃), 2.30(s, 3H, FurCH ₃)
11	8.15(d, 1H, Fur-H), 7.93(d, 2H, Ar-H), 7.57(m, 1H, Ar-H), 5.76 (s, 2H, NH ₂), 4.91(s, 2H, CH ₂), 6.67(t, 1H, Fur-H)
12	8.13(d, 1H, Fur-H), 7.82(d, 2H, Ar-H), 7.08(d, 2H, Ar-H), 4.91 (s, 2H, CH ₂), 5.77(s, 2H, NH ₂), 3.82(s, 3H, OCH ₃)

Finally passing of reaction of cyclization and formations of derivative 6-aryl-7H-[1,2,4]-triazolo-[3,4-b]-[1,3,4]-thiadiazines (scheme 1) it is well-proven by us by X-ray structured researches (pic. 1).

In connection with difficulties which arose up at «growing» of crystal, product of co-operation of 5-(2-methylfuran-3-yl)-4-amino-1,2,4-triazole-3-thiol is investigated with equivalent amount of 2-bromine-1-(4-methoxyphenylethanone). Therefore the final product shows by itself a bromide organic cation (pic. 1).

Positive charge of cation is localized on the atom of N (2) of 1,2,4-triazole cycle which forms single connection of N (2) of -N (3) 1.372 (6) Å (average meaning 1.366 Å) and double connection of N (2) of -C (1) 1.309 (6) Å (average meaning 1.298 Å), and Hydrogen atom is discovered in the difference of synthesis of electronic closeness. Cation is related to the anion of bromide hydrogen connection of N (2) of -H ... Br (1) 'H ... Br 2.42 Å NH ... Br 160 °. Thiadiazine heterocycle of cation is in conformation which is intermediate between twist- bath and sofa (parameters of composition: S = 0.66, È = 60.8, Ø = 24.3). Deviations of atoms of Ñ (3) and Ñ (4) from the mediumquadratic square of other atoms of cycle is 1.00 Å and 0.46 Å, accordingly. Pushing away between a para-methoxyphenyl substitute and thiadiazine cycle (the shorten intramolecular contacts of H (3b) ... C (6) 2.58 Å (sum of vandervaalsov radiuses 2.87 Å), H (3b) ... H (6a) 2.01 Å (2.34 Å), H (6) ... C (3) 2.71 Å (2.87 Å), H (10) ... N (4) 2.41 Å (2.67 Å)) results to the turn of aromatic cycle relatively endocycle double connection of C (4) of -N (4) (torsin angle of N (4) of -C (4) -C (5) -C (10) 13.6 (7) °). Methoxygroup is coplanared to the square of aromatic cycle (torsin angle of C (11) of -O (2) -C (8) -C (7) -1 (1)), without regard to pushing away between the atoms of methyl group and by the atoms of cycle (the shorten contacts (7) ... Ñ (11) 2.56 Å (2.87 Å), Í (7) ... Í (11c) 2.22 Å (2.34 Å), Í (11c) ... Ñ (7) 2.65 Å (2.87 Å)). Furan cycle is notably unfolded in relation to a triazole cycle (torus angle of N (2) of -C (1) -C (12) -C (15) 40.0 (9) °). In a crystal between molecules found out cation and anion S-N ... Br intermolecular water connections: C (3) of -H (3a) ... Br (1) '(x-1, in, z) H ... B of r 2.99 Å CH ... Br 136 °; C (3) of -H (3b) ... Br (1) '(-

1.5 + x, to 0.5th, -0.5 + z) H. .. Br 2.93 Å CH ... Br 165 °; C (6) of -H ... Br (1) '(-1.5 + x, to 0.5th, -0.5 + z) H. .. Br 2.88 Å CH ... Br 171 °; C (11) of -H (11b) ... Br (1) '(x-2, in, z-1) H. .. Br 2.87 Å CH ... Br 161; C (14) of -H ... Br (1) '(2th, to th, 1-z) H. .. Br 2.91 Å CH ... Br 161. In addition, distance of Br (1) ... S (1) '(-0.5 + x, to 0.5th, -0.5 + z) 3.63 Å less than sum of vandervaalsov radiuses, that allows to interpret this shorten contact as δ -hole cooperation between a positive charge during connection of C (3) of -S (1) and indivisible pair of bromine.

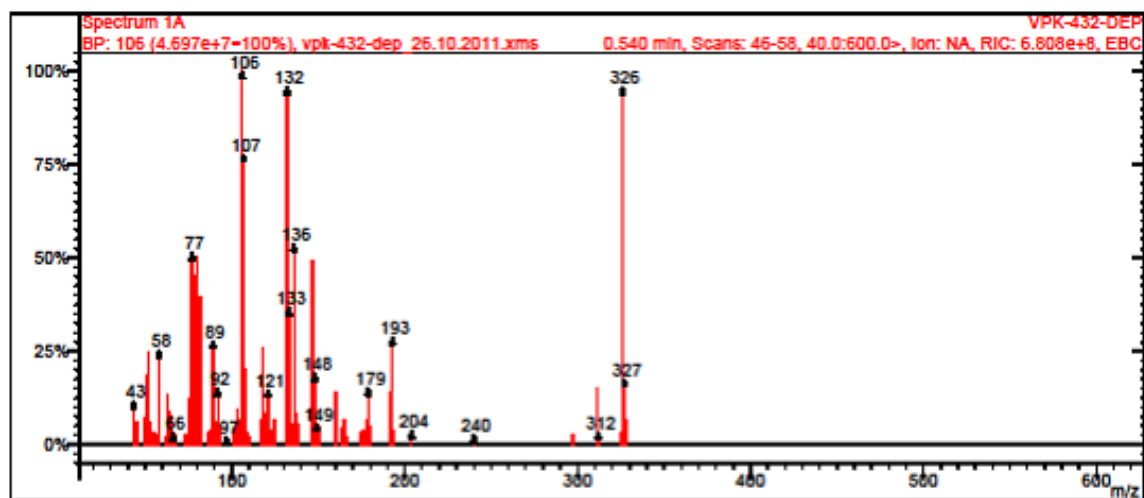


Pic. 1. X-raystructural research of 3-(2-methylfuran-3-yl)-6-(4-methoxyphenyl)-7H-(1,2,4-triazolo)-(3,4-b)-(1,3,4-thiodiazine) (10).

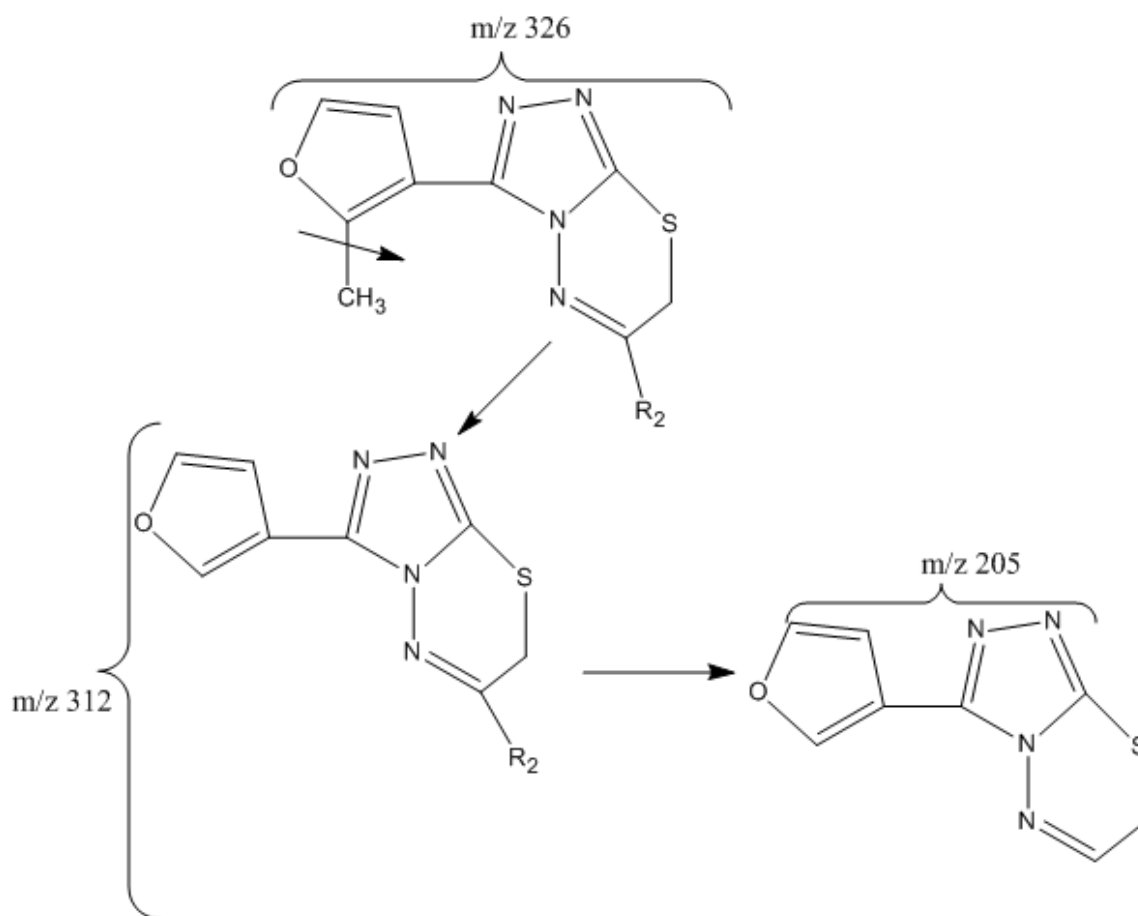
Crystals are monocyclic compounds, $C_{16}H_{15}N_4O_2SBr$, at 20°C $a = 6.6540(8)$, $b = 24.116(3)$, $c = 10.785(2)$ Å $\beta = 100.32(1)^\circ$ $V = 1702.6(4)$ Å³, $M_r = 407.29$, $Z = 4$, space group P21/n, $d = 1.589$ g/sm $\mu(MOK_\alpha) = 2.553$ mm⁻¹, $F(000) = 824$. Parameters of elementary cells and intensity 20888 reflections (9377 independent, $R_{int} = 0.074$) measured on a diffractometer «Xcalibur-3» (MOK α radiation, CCD-detector, graphite monochromator, screening, $2\theta_{max} = 50$).

Individuality of the synthesized compounds (3-12, table 1) is confirmed chromatographically. At chromatography 3-(2-methylfuran-3-yl)-6-(4-

methoxyphenyl)-7H-(1,2,4-triazolo)-(3,4-b) -(1,3,4-thiodiazine) found out a clear peak which testifies to individuality of the standard of substance (pic. 2).



Pic. 2. Chromato-mass spectrum of 3-(2-methylfuran-3-yl)-6-(4-methoxyphenyl)-7H-(1,2,4-triazolo)-(3,4-b) -(1,3,4-thiodiazine) (10).



Scheme 2. Fragmentation pattern of the s-triazole and its derivatives

Investigating fragmentation of molecule of 3-(2-methylfuran-3-yl)-6-(4-methoxyphenyl)-7H-(1,2,4-triazolo)-(3,4-b) -(1,3,4-thiodiazine) (gross-formula of C₁₆H₁₄N₄O₂S, M.m=326 of à.o.m.) (scheme 2) is established that destruction of compounds passes with formation of a fragment (m/z 312) which in future is destroyed with formation of a fragment from (m/z 205), that confirms the structure of molecule of 3-(2-methylfuran-3-yl)-6-(4-methoxyphenyl)-7H-(1,2,4-triazolo)-(3,4-b) -(1,3,4-thiodiazine).

CONCLUSIONS. The row of new derivatives of 1,2,4-triazolo-(3,4-b)-1,3,4-thiodiazine is synthesized with residues of fragments of furan nucleus. The structure of new potential bioactive compounds is confirmed by modern physical and chemical methods.

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