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SYNTHESIS OF 1H-1,2,3-TRIAZOLE DERIVATIVES BY THE CYCLIZATION OF ARYL AZIDES WITH 2-BENZOTHIAZOLYLACETONONE, 1,3-BENZO-THIAZOL-2-YLACETONITRILE, AND (4-ARYL-1,3-THIAZOL-2-YL)ACETONITRILES

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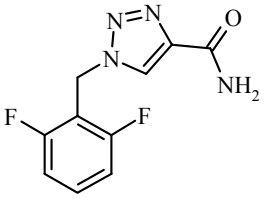
The cyclization of aryl azides with 2-benzothiazolylacetone, 1,3-benzothiazol-2-ylacetonitrile, and (4-aryl-1,3-thiazol-2-yl)acetonitriles in methanol in the presence of sodium methylate gives high yields of new products, 2-(5-methyl(amino)-1-aryl-1H-1,2,3-triazol-4-yl)-1,3-benzothiazoles and 1-aryl-(4-aryl-1,3-thiazol-2-yl)-1H-1,2,3-triazole-5-amines. 1,3-Benzothiazol-2-ylacetonitrile undergoes an anionic domino reaction with methyl 2-azidobenzoate or 2-azidobenzonitrile to give [1,2,3]triazolo[1,5-a]quinazoline derivatives.

Keywords: 1,3-benzothiazole derivatives, 1,3-thiazole derivatives, tetrazole, 1H-1,2,3-triazole, [1,2,3]triazolo[1,5-*a*]quinazoline, heterocyclization, domino reaction.

Functionalized 1,2,3-triazoles have a broad range of biological activity although these compounds are not encountered in natural products. The cephalosporin antibiotic *cefatricin* is an efficient drug for countering agents leading to diseases in the respiratory tract, connective tissue, and skin [2, 3]. Difluoride **I** is an anticonvulsive agent, compounds **II** displays anti-HIV activity [5], while compounds **III** play an important role in the treatment of Alzheimer's disease as well as type-1 and type-2 diabetes [6]. Some 1,2,3-triazoles act as antagonists of the GABA receptor [7, 8], agonists of muscarine receptors [9], neuroleptics [11], antihistaminics [12], and antiproliferative agents [13].



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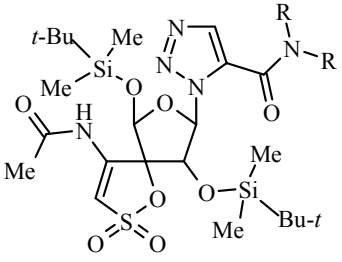

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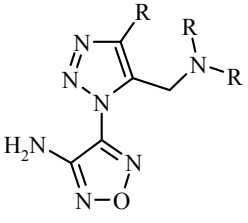

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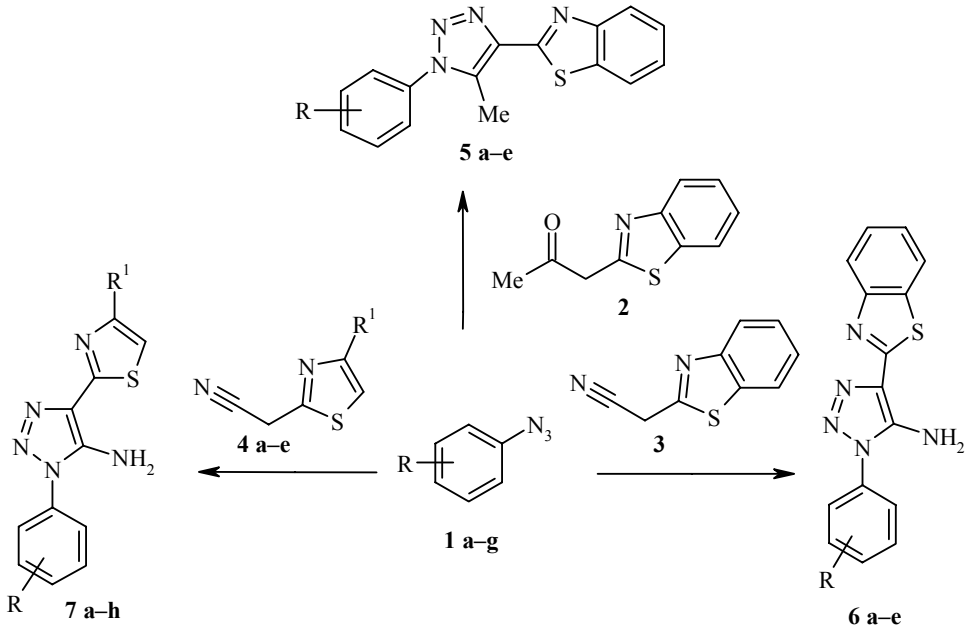
A good method for the synthesis of 1H-1,2,3-triazole derivatives involves the reaction of aryl azides with CH-active compounds containing a COR or C≡N group [14]. However, the scope for the preparative application of this method has not been elucidated due, in part, to competing reactions. For example, the partial reduction of the azido group to an amino group occurs in some cases under the conditions of this reaction [14]. The reaction of azides with α-methylene ketones and acetonitriles activated by an aryl or hetaryl substituent holds promise as a synthetic method. Only a few examples have been reported for the reaction of aryl azides with arylacetonitriles and phenylacetone [14, 15] leading to 5-aminomethyl-1,4-diaryl-1H-1,2,3-triazoles. The introduction of a heterocyclic substituent at C-4 of the triazole ring might be expected to expand the biological activity of these compounds.

We investigated the reaction of aryl azides **1a-i** with 1,3-benzothiazol-2-ylacetone (**2**), 1,3-benzothiazol-2-ylacetonitrile (**3**), and 4-R^1-thiazolylacetonitriles **4a-e** obtained according to reported procedures [16-18].

We found that compound **2-4** react with aryl azides to give triazole derivatives **5-7** (Tables 1 and 2) with a heterocyclic substituent at C-4.



1 a R = H, **b** R= 2-Me, **c** R = 3-Me, **d** R = 4-Me, **e** R = 4-F, **f** R = 4-NO_2, **g** R = 4-COOH;
5 a R = H, **b** R = 2-Me, **c** R = 4-Me, **d** R = 4-NO_2, **e** R = 4-COOH; **6 a** R = H, **b** R = 3-Me,
c R = 4-Me, **d** R = 4-F, **e** R = 4-NO_2; **4 a** R^1 = Ph, **b** R^1 = 4-MeC_6H_4, **c** R^1 = 4-FC_6H_4,
d R^1 = 4-ClC_6H_4, **e** R^1 = 2-naphthyl; **7 a–e** R = H, **a** R^1 = Ph, **b** R^1 = 4-MeC_6H_4, **c** R^1 = 4-FC_6H_4,
d R^1 = 4-ClC_6H_4, **e** R^1 = 2-naphthyl, **f** R = Me, **g** R = F, **h** R = 4-NO_2, **f–h** R^1 = Ph

The reaction of aryl azide **1** with 2-benzothiazolylacetone **2** is complete in a few minutes upon heating or after 1 h at room temperature. Triazole derivatives **6a-e** were obtained in the reaction of aryl azides with 1,3-benzothiazol-2-ylacetonitrile **3** after 1 min at room temperature. Products of the Dimroth rearrangement and reduction of the azide group from the reaction mixture were not isolated from the reaction mixture. Thus, these reactions are a good method for the synthesis of triazole derivatives with a benzothiazole substituent at C-4. (4-R^1-1,3-thiazol-2-yl)acetonitriles **4a-e** also react with aryl azides without complications; the yields of cyclization products **7** ranged from 66 to 93%.

The use of aryl azides **1h**,**i** containing a nitrile or ester group in the *ortho* position to the azido group in the abovementioned reactions permits anionic domino reaction [19] of these azides with 1,3-benzothiazol-2-ylacetonitrile **3**. In both cases, the amino group at C-5 in the triazole ring formed in the first step reacts with

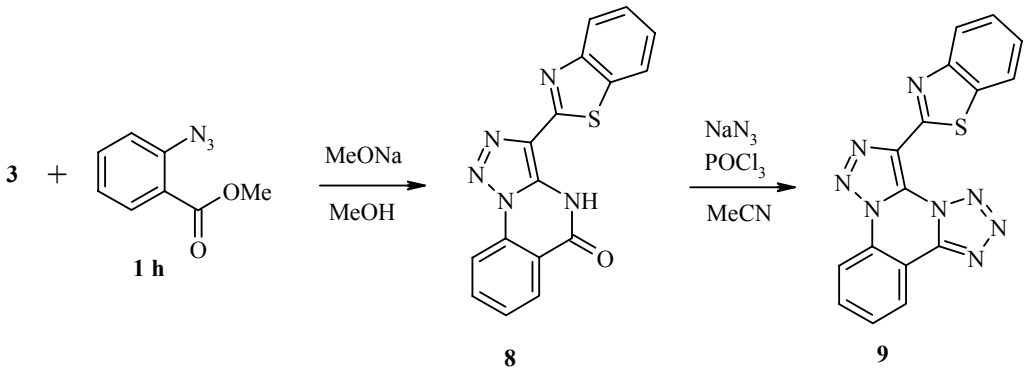


TABLE 1. Characteristics of Products **5-10**

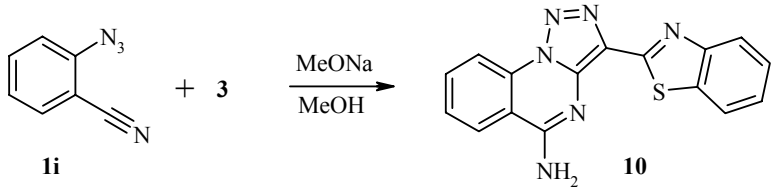
Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
5a	$C_{16}H_{12}N_4S$	65.80 / 65.73	4.05 / 4.14	19.07 / 19.16	147-148	81
5b	$C_{17}H_{14}N_4S$	66.50 / 66.64	4.52 / 4.61	18.19 / 18.29	145-146	74
5c	$C_{17}H_{14}N_4S$	66.72 / 66.64	4.70 / 4.61	18.17 / 18.29	171-172	88
5d	$C_{16}H_{11}N_5O_2S$	56.84 / 56.96	3.19 / 3.29	20.67 / 20.76	223-224	94
5e	$C_{17}H_{12}N_4O_2S$	60.35 / 60.70	3.68 / 3.60	16.72 / 16.66	>300	72
6a	$C_{15}H_{11}N_5S$	61.26 / 61.42	3.85 / 3.78	23.75 / 23.87	227-228	82
6b	$C_{16}H_{13}N_5S$	62.69 / 62.52	4.15 / 4.26	22.93 / 22.78	188-189	77
6c	$C_{16}H_{13}N_5S$	62.37 / 62.52	4.18 / 4.26	22.66 / 22.78	231-232	85
6d	$C_{15}H_{10}FN_5S$	57.93 / 57.87	3.06 / 3.24	22.59 / 22.49	247-248	93
6e	$C_{15}H_{10}N_6O_2S$	53.21 / 53.25	3.08 / 2.98	24.72 / 24.84	259-260	91
7a	$C_{17}H_{13}N_5S$	63.76 / 63.93	4.07 / 4.10	21.80 / 21.93	151-152	65
7b	$C_{18}H_{15}N_5S$	64.95 / 64.84	4.45 / 4.53	20.88 / 21.01	199-200	80
7c	$C_{17}H_{12}FN_5S$	60.63 / 60.52	3.50 / 3.59	20.84 / 20.76	167-168	71
7d	$C_{17}H_{12}ClN_5S$	57.43 / 57.71	3.33 / 3.42	19.72 / 19.79	206-205	82
7e	$C_{21}H_{15}N_5S$	68.39 / 68.27	4.01 / 4.09	19.02 / 18.96	174-175	76
7f	$C_{18}H_{15}N_5S$	64.72 / 64.84	4.58 / 4.53	20.93 / 21.01	196-197	66
7g	$C_{17}H_{12}FN_5S$	60.40 / 60.52	3.45 / 3.59	20.42 / 20.76	194-195	87
7h	$C_{17}H_{12}N_6O_2S$	56.10 / 56.04	3.20 / 3.32	22.94 / 23.06	291-292	73
8	$C_{16}H_9N_5OS$	60.27 / 60.18	2.78 / 2.84	21.82 / 21.93	>300	84
9	$C_{16}H_8N_8S$	55.67 / 55.81	2.41 / 2.34	32.36 / 32.54	221-222	93
10	$C_{16}H_{10}N_6S$	60.08 / 60.36	3.27 / 3.17	26.25 / 26.40	>300	91

TABLE 2. ^{1}H NMR spectra of Compounds **5-10**

Com-pound	Chemical shifts, δ, ppm (*J*,Hz)
1	2
5a	2.82 (3H, s, CH_3); 7.43 (1H, m, benzothiazole H-5); 7.49 (1H, m, benzothiazole H-6); 7.60-7.68 (5H, m, C_6H_5); 7.99 (1H, d, ^3J = 8.0, benzothiazole H-4); 8.06 (1H, d, ^3J = 7.6, benzothiazole H-7)
5b	2.10 (3H, s, CH_3); 2.61 (3H, s, CH_3); 7.39-7.57 (6H, m, Ar); 7.97 (1H, d, ^3J = 8.0, benzothiazole H-4); 8.05 (1H, d, ^3J = 8.0, benzothiazole H-7)
5c	2.48 (3H, s, CH_3); 2.78 (3H, s, CH_3); 7.42 (1H, m, benzothiazole H-5); 7.43 (2H, d, ^3J = 8.0, H_{Ar}-3,5); 7.49 (1H, m, benzothiazole H-6); 7.51 (2H, d, ^3J = 8.0, H_{Ar}-2,6); 7.97 (1H, d, ^3J = 8.0, benzothiazole H-4); 8.04 (1H, d, ^3J = 8.0, benzothiazole H-7)
5d	2.90 (3H, s, CH_3); 7.44 (1H, m, benzothiazole H-5); 7.52 (1H, m, benzothiazole H-6); 8.01 (1H, d, ^3J = 8.4, benzothiazole H-4); 8.05 (1H, d, ^3J = 8.4, benzothiazole H-7); 8.07 (2H, d, ^3J = 8.8, H_{Ar}-2,6); 8.50 (2H, d, ^3J = 8.8, H_{Ar}-3,5)
5e	2.86 (3H, s, CH_3); 7.44 (1H, m, benzothiazole H-5); 7.52 (1H, m, benzothiazole H-6); 7.81 (2H, d, ^3J = 8.8, H_{Ar}-2,6); 8.01 (1H, d, ^3J = 8.0, benzothiazole H-4); 8.07 (1H, d, ^3J = 7.6, benzothiazole H-7); 8.22 (2H, d, ^3J = 8.8, H_{Ar}-3,5); 13.07 (1H, br. s, COOH)
6a	6.78 (2H, s, NH_2); 7.34 (1H, m, benzothiazole H-6); 7.45 (1H, m, benzothiazole H-5); 7.54 (1H, m, H_{Ph}-4); 7.63 (2H, m, H_{Ph}-3,5); 7.68 (2H, d, ^3J = 7.6, H_{Ph}-2,6); 7.93 (1H, d, ^3J = 8.4, benzothiazole H-7); 7.99 (1H, d, ^3J = 8.0, benzothiazole H-4)
6b	2.49 (3H, s, CH_3); 6.78 (2H, s, NH_2); 7.33-7.38 (2H, m, benzothiazole H-6 + H_{Ar}); 7.41-7.54 (4H, m, benzothiazole H-5 + H_{Ar}); 7.93 (1H, d, ^3J = 8.0, benzothiazole H-7); 8.00 (1H, d, ^3J = 8.0, benzothiazole H-4)
6c	2.46 (3H, s, CH_3); 6.70 (2H, s, NH_2); 7.34 (1H, m, benzothiazole H-6); 7.39-7.47 (3H, m, benzothiazole H-5 + H_{Ar}-3,5); 7.53 (2H, d, ^3J = 8.0, H_{Ar}-2,6); 7.92 (1H, d, ^3J = 8.4, benzothiazole H-7); 7.98 (1H, d, ^3J = 8.0, benzothiazole H-4)
6d	6.79 (2H, s, NH_2); 7.35 (1H, m, benzothiazole H-6); 7.41 (2H, m, H_{Ar}-3,5); 7.46 (1H, m, benzothiazole H-5); 7.70 (2H, dd, $J_{H,H}$ = 8.8, $J_{H,F}$ = 4.8, H_{Ar}-2,6); 7.93 (1H, d, ^3J = 8.0, benzothiazole H-7); 8.00 (1H, d, ^3J = 8.0, benzothiazole H-4)
6e	7.08 (2H, s, NH_2); 7.36 (1H, m, benzothiazole H-6); 7.47 (1H, m, benzothiazole H-5); 7.95 (1H, d, ^3J = 8.0, benzothiazole H-7); 7.99 (1H, d, ^3J = 7.6, benzothiazole H-4); 8.02 (2H, d, ^3J = 8.8, H_{Ar}-2,6); 8.46 (2H, d, ^3J = 8.8, H_{Ar}-3,5)
7a	6.56 (2H, s, NH_2); 7.32 (1H, m, H_{Ph}-4); 7.43 (2H, t, ^3J = 7.6, H_{Ph}-3,5); 7.54 (1H, m, H_{PhN}-4); 7.63 (2H, m, H_{PhN}-3,5); 7.69 (2H, d, ^3J = 8.0, H_{PhN}-2,6); 7.77 (1H, s, thiazole); 7.99 (2H, d, ^3J = 7.2, H_{Ph}-2,6)
7b	2.38 (3H, s, CH_3); 6.55 (2H, s, NH_2); 7.22 (2H, d, ^3J = 8.0, H_{Ar}-3,5); 7.53 (1H, m, H_{Ph}-4); 7.63 (2H, m, H_{Ph}-3,5); 7.68 (2H, d, ^3J = 8.0, H_{Ar}-2,6); 7.70 (1H, s, thiazole); 7.86 (2H, d, ^3J = 8.0, H_{Ph}-2,6)
7c	6.55 (2H, s, NH_2); 7.18 (2H, t, ^3J = 8.8, H_{Ar}-3,5); 7.53 (1H, m, H_{Ph}-4); 7.63 (2H, m, H_{Ph}-3,5); 7.68 (2H, d, ^3J = 7.6, H_{Ph}-2,6); 7.77 (1H, s, thiazole); 8.04 (2H, dd, $J_{H,F}$ = 5.2, $J_{H,H}$ = 8.8, H_{Ar}-2,6)
7d	6.55 (2H, s, NH_2); 7.43 (2H, d, ^3J = 8.8, H_{Ar}-3,5); 7.53 (1H, m, H_{Ph}-4); 7.63 (2H, m, H_{Ph}-3,5); 7.67 (2H, d, ^3J = 7.6, H_{Ph}-2,6); 7.86 (1H, s, thiazole); 8.02 (2H, d, ^3J = 8.8, H_{Ar}-2,6)
7e	6.64 (2H, s, NH_2); 7.45-7.51 (2H, m, naphthyl); 7.54 (1H, m, H_{Ph}-4); 7.64 (2H, m, H_{Ph}-3,5); 7.70 (2H, d, ^3J = 7.2, H_{Ph}-2,6); 7.86 (1H, d, ^3J = 6.8, naphthyl); 7.92 (1H, d, ^3J = 8.8, naphthyl); 7.95 (1H, s, thiazole); 7.97 (1H, d, ^3J = 8.8, naphthyl); 8.12 (1H, dd, ^3J = 8.8, ^4J = 1.6, naphthyl); 8.56 (1H, s, naphthyl)
7f	2.47 (3H, s, CH_3); 6.47 (2H, s, NH_2); 7.32 (1H, m, H_{Ph}-4); 7.40-7.46 (4H, m, H_{Ph}-3,5 + H_{Ar}-3,5); 7.55 (2H, d, ^3J = 7.6, H_{Ar}-2,6); 7.76 (1H, s, thiazole); 7.99 (2H, d, ^3J = 8.0, H_{Ph}-2,6)
7g	6.56 (2H, s, NH_2); 7.33 (1H, m, H_{Ph}-4); 7.38-7.46 (4H, m, H_{Ph}-3,5 + H_{Ar}-3,5); 7.71 (2H, dd, $J_{H,H}$ = 8.0, $J_{H,F}$ = 4.8, H_{Ar}-2,6); 7.80 (1H, s, thiazole); 8.00 (2H, d, ^3J = 7.6, H_{Ph}-3,5)
7h	6.85 (2H, s, NH_2); 7.33 (1H, m, H_{Ph}-4); 7.44 (2H, m, H_{Ph}-3,5); 7.81 (1H, s, thiazole); 7.98-8.04 (4H, m, H_{Ph}-2,6 + H_{Ar}-2,6); 8.46 (2H, d, ^3J = 8.8, H_{Ar}-3,5)

TABLE 2 (continued)

1	2
8	7.27 (1H, m, quinozaline); 7.41 (1H, m, benzothiazole H-6); 7.49 (1H, m, benzothiazole H-5); 7.74 (1H, m, quinozaline); 7.90-7.99 (2H, m, quinozaline + benzothiazole H-4); 8.17-8.25 (2H, m, quinozaline + benzothiazole H-7)
9	7.44 (1H, m, benzothiazole H-6); 7.54 (1H, m, benzothiazole H-5); 7.96 (1H, m, H_{Ar}-4); 8.08 (1H, d, ^3J = 8.0, benzothiazole H-7); 8.13 (1H, d, ^3J = 8.0, benzothiazole H-4); 8.26 (1H, m, H_{Ar}-5); 8.44 (1H, d, ^3J = 8.4, H_{Ar}-6); 8.75 (1H, d, ^3J = 8.0, H_{Ar}-3)
10	7.35 (1H, m, benzothiazole H-6); 7.45 (1H, m, benzothiazole H-5); 7.70 (1H, m, H_{Ar}-4); 7.95 (1H, d, ^3J = 7.6, benzothiazole H-7); 7.97-8.02 (2H, m, benzothiazole H-4 + H_{Ar}-5); 8.35 (2H, br. s, NH_2); 8.45 (1H, d, ^3J = 8.0, C_6H_4 H_{Ar}-3); 8.50 (1H, d, ^3J = 7.6, H_{Ar}-6)



the *ortho* substituent (C≡N or CO_2Me) to give the [1,2,3]triazolo[1,5-*a*]quinazoline system (compounds **8** and **10**, Tables 1 and 2). The domino reaction takes place in a few minutes with a good yield of the reaction products when there is an ester or nitrile group in the starting azide.

Benzothiazole derivative **8** is transformed by the action of $POCl_3$ and sodium azide in acetonitrile in one step to give 5-(1,3-benzothiazol-2-yl)tetrazolo[1,5-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (**9**) (Tables 1 and 2).

Thus, we have shown that 2-benzothiazolylacetone **2**, 1,3-benzothiazol-2-ylacetonitrile **3**, and (4-aryl-1,3-thiazol-2-yl)acetonitriles **4** are convenient reagents for the synthesis of 1H-1,2,3-triazole derivatives.

EXPERIMENTAL

The ^{1}H NMR spectra were taken on a Mercury 400 spectrometer at 400 MHz in DMSO-d_6. The chemical shifts are given relative to TMS.

Azides **1a-i** were obtained by a method similar to a reported procedure [20]. Samples of 2-benzothiazolylacetone **2** [16], 1,3-benzothiazol-2-ylacetonitrile **3** [17], and 4-R-thiazolylacetonitriles **4a-e** [18] were obtained according to reported procedures.

2-[5-Methyl-1-(R-phenyl)-1H-1,2,3-triazol-4-yl]-1,3-benzothiazoles 5a-e (General Method). A solution of sodium (0.3 g, 13 mmol) in methanol (20 ml) was added with cooling to a solution of the corresponding aryl azide **1** (10 mmol). Then, 2-benzothiazolylacetone **2** (1.9 g, 10 mmol) was added with vigorous stirring. The mixture was heated for 30 min and cooled to room temperature. The precipitate formed was filtered off and purified by recrystallization from ethanol.

Synthesis of Compounds 6-8 and 10 (General Method). Hetarylacetonitrile **3** or **4** (10 mmol) and aryl azide **1** (10 mmol) were added with vigorous stirring to a solution of sodium methylate obtained from 0.3 g sodium and 20 ml methanol. The mixture was stirred at room temperature until formation of a precipitate, which was filtered off and purified by recrystallization from ethanol–DMF.

5-(1,3-Benzothiazol-2-yl)tetrazolo[1,5-*c*][1,2,3]triazolo[1,5-*a*]quinazoline (9). A mixture of compound **8** (0.64 g, 2 mmol), NaN_3 (0.26 g, 4 mmol), and $POCl_3$ (1.54 g, 10 mmol) in acetonitrile (20 ml) was heated at reflux with stirring for 10 h. The solvent and excess $POCl_3$ were distilled off at reduced pressure. The residue was cooled and neutralized by adding saturated aqueous $NaHCO_3$. The precipitate formed was filtered off and crystallized from ethanol–DMF.

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