Synthesis of [1,2,4]triazolo[4,3-*b*]-*s*-tetrazines with incorporated furazan ring

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Furazancarboxylic hydrazides can serve as nucleophiles to substitute for one dimethylpyrazole fragment in bis(3,5-dimethylpyrazol-1-yl)-*s*-tetrazine, giving the corresponding *N*′-[6-(3,5-dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-*R*-furazan-3-carbohydrazides in good yields. Dehydration of the indicated carbohydrazides in polyphosphoric acid for the first time gave rise to [1,2,4]triazolo[4,3-*b*]-*s*-tetrazines containing the furazan ring as a substituent at the triazole ring.

Key words: furazan, triazole, tetrazine, triazolo[4,3-*b*]-*s*-tetrazine, cyclocondensation, nucleophilic substitution, solvent effects, X-ray diffraction analysis.

1,2,4,5-Tetrazine ring (*s*-tetrazine) can be annulated with various five- and six-membered heterocycles, that is in detail summarized in the recent review.[1] The bicyclic system of [1,2,4]triazolo[4,3-*b*]-*s*-tetrazine is of potential interest as a basic framework for the design of compounds exhibiting a wide range of practically useful properties; depending on the type of substituents, they can be, for example, biologically active compounds[2] or high-energy materials.[3]

Such a bicyclic system, as a rule, is formed by annulation of a 1,2,4-triazole ring to the *s*-tetrazine one. In this case, 3-hydrazino-*s*-tetrazines are used as the starting compounds,[4] which are cyclized by such reagents, as formic acid,[5] ortho esters,[5–8] imino esters,[5] bromocyan,[6] or carbon disulfide.[5] At the same time, hydrazinotetrazines can be initially involved into the reaction with aldehydes to form the corresponding hydrazones, which cyclize to triazolo[4,3-*b*]-*s*-tetrazines upon the action of such oxidants, as $Pb(OAc)_4$ or Bu^tOCl,[5] or thermally.[9]

According to the recent studies,[4] hydrazinotetrazine acyl derivatives can be obtained by nucleophilic substitution for the dimethylpyrazole fragment in the easily available 3,6-bis(3,5-dimethylpyrazol-1-yl)-*s*-tetrazine **1a** (see Ref. 10), in which case hydrazides of benzoic and nicotinic acids were successfully used as the nucleophiles. In continuation of our works on the construction of compounds including *s*-tetrazine and furazan (1,2,5-oxadiazole) rings,[11] we considered it reasonable to study a possibility of using furazancarboxylic hydrazides **2** for the synthesis of the corresponding triazolo[4,3-*b*]-*s*-tetrazines.

The Taft induction constants (σ*) of 4-R-furazanyl groups as substituents are within the interval from 2.55 to 2.88 (with R = NH_2 and NO_2, respectively).[12] This index for such a substituent as a CF_3 group is the closest to that of furazanyl fragment (σ* = 2.6).[13] Therefore, initially we attempted to find conditions under which available *N*′-[6-(3,5-dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]trifluoromethyl-3-carbohydrazide **3** (see Ref. 4) could have cyclize to the corresponding (trifluoromethyl)triazolotetrazine **4a**. Note that the preceding attempts to cyclize hydrazinotetrazine acyl derivatives under mild conditions failed,[5] at the same time, cyclization of hydrazinoazine acyl derivatives is widely used for the construction of various [1,2,4]triazolo[4,3-*b*]azines.[14–17] In fact, the studies performed showed that compound **3** is efficiently dehydrated by a short-time heating in polyphosphoric acid, and the desired bicycle **4a** is formed in ~80% yield (Scheme 1).

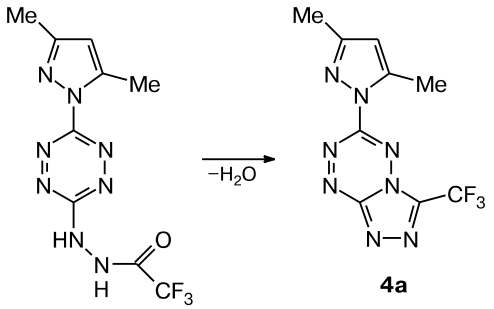
In the azole series, the furazan ring as a substituent is known to have one of the most powerful electron-withdrawing effects.[18—21] Naturally, the nucleophilicity of molecules bearing this substituent is decreased. Will the dimethylpyrazole fragment in tetrazine **1** undergo nucleophilic substitution by the furazancarboxylic hydrazides?

To answer this questiion, we studied a reaction of compound **1a** with 3-methylfurazancarboxylic hydrazide **2a** (see Ref. 22) as the model reaction (Scheme 2). We started with clarification of the issue whether the type of a solvent influences the reaction result. A typical procedure consisted in heating a mixture of the equimolar amounts of reac-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 1, pp. 119—128, January, 2012.

1066-5285/12/6101-121

Scheme 1



3 **4a**

tants (the molar concentration of 0.1 mol L^{-1}) in a solvent (Table 1). The reaction was carried out until the starting reagents or one of them were completely consumed, that was monitored by TLC (but no longer than 55 h).

It turned out that substitution for one of the dimethylpyrazole fragments to form the product **5a** is observed in all the solvents studied. As it is seen from Table 1, from 2 to 55 h is required to bring the reaction to completion depending on the type of a solvent. The nucleophilic substitution is the fastest in alcohols. However, in this case alcohols are also involved as competing nucleophiles, that leads to the formation of a mixture of the target product **5a** with the corresponding alkoxytetrazines **8a**—**c**; formation of methoxy derivative **8a** has been observed earlier[4] in the reaction of compound **1a** with (cyclo)alkylamines in methanol.

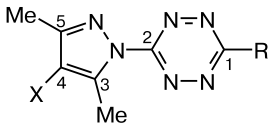
It should be noted that alkoxytetrazines **8a**—**c** are well soluble in weakly polar solvents, this enables their easy isolation from compound **5a**, which is soluble only in polar

Table 1. Effect of solvents on the reaction between compounds **1a** and **2a**

Entry	Solvent	*T* /°C	τ^a/h	Yield of **5a** (%)	Other products (yield (%))
1	MeOH	64	2	40	**8a** (29)
2	EtOH	78	2	47	**8b** (20)
3	Pr^iOH	82	3	80	**8c** (5)
4	DMFA	90	4	78	**8d** (10)
5	Benzene	80	5	76	—
6	Dioxane	85	6	60	—
7	Glyme	80	18	86	—
8	DMSO	80	23	62	—
9	[emim][BF_4]^b	80	24	86	—
10	THF	66	26	75	—
11	$MeNO_2$	80	36	58	—
12	$HCCl_3$	61	54	28	**1a** (43) + + **2a** (30)
13	H_2O	80	55	6	**1a** (67) + + **2a** (61) + + **8e** (7)
14	MeCN	82	55	88	—

^{a} The reaction time.

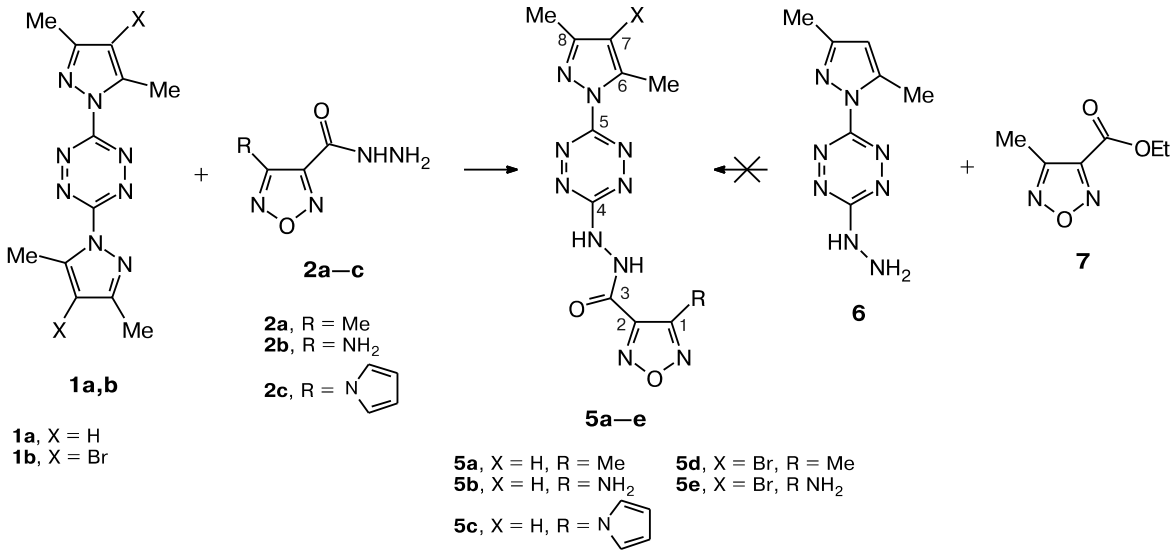
^{b} [emim][BF_4] is the 4-ethyl-1-methylimidazolium tetrafluoroborate.



8a—g

X = H (**a**—**e**), Br (**f**, **g**)
R = OMe (**a**), OEt (**b**, **f**), OPr^i (**c**, **g**), NMe_2 (**d**), OH (**e**)

Scheme 2



1a,b

1a, X = H
1b, X = Br

2a—c

2a, R = Me
2b, R = NH_2
2c, R =

5a—e

5a, X = H, R = Me
5b, X = H, R = NH_2
5c, X = H, R =
5d, X = Br, R = Me
5e, X = Br, R NH_2

6

7

solvents. Thus, simple treatment of a mixture of compounds **5a** and **8a—c** with hot hexane, which dissolves alkoxy derivative **8a—c**, provides an opportunity to quantitatively separate these products.

Despite the fact that DMF was freshly dried and distilled, the reaction of tetrazine **1a** and hydrazide **2a** was accompanied by a side formation of the dimethylamine derivative **8d** (see Table 1, entry *4*).

The poor solubility of compound **1a** in water strongly interferes with the reaction course. After heating for 55 h, about half of unreacted starting reactants were isolated, and, besides the target product, the hydroxy derivative **8e** was also formed (see Table 1, entry *13*).

The maximum yield (see Table 1, entry *9*) was obtained when the reaction was carried out in the ionic liquid (4-ethyl-1-methylimidazolium tetrafluoroborate, [emim][BF_4]), however, the reaction is slow in this medium.

No substitution for the second dimethylpyrazole fragment on the tetrazine ring was detected in any of the solvents listed in Table 1, even when a three-fold excess of hydrazide **2a** and an increase in the heating time were used.

Attempts to obtain the acyl derivative **5a** by a prolonged heating of hydrazinotetrazine **6** and 3-methylfurazancarboxylic ester **7** (see Scheme 2) at 100 °C in dioxane or toluene failed.

It is known[4,23] that introduction of a bromine atom in position 4 of the pyrazole fragment facilitates substitution for this fragment on the tetrazine ring by the action of some nucleophiles. In fact, in ethanol and isopropanol the reaction of 3,6-bis(4-bromo-3,5-dimethylpyrazol-1-yl)-*s*-tetrazine **1b** with hydrazide **2a** (see Scheme 2) is faster, however, amount of the side product **8f**,**g** increases, too (*cf.* Tables 1 and 2). Introduction of a bromine atom into the molecule decreases the solubility of compound **1b** in a number of solvents. Apparently, this is the fact that strongly retards substitution in such solvents as MeCN, glyme, and chloroform (see Table 2, entries *15*, *18*, and *19*). Only in DMSO the switch from compound **1a** to **1b** is accompanied by significant acceleration of the reaction (about tenfold) and increase in the yield of monosubstituted product (see Table 2, entry *20*); the disubstituted product was not detected in this case, either.

Table 2. Effect of solvents on the reaction between compounds **1b** and **2a**

Entry	Solvent	*T*/°C	τ^a/h	Yield of **5d** (%)	P [b] (yield (%))
15	MeCN	80	55.00	7	**1b** (78)
16	EtOH	80	0.66	40	**8f** (30)
17	Pr^iOH	80	2.00	63	**8g** (10)
18	$CHCl_3$	65	54.00	5	**1b** (62)
19	Glyme	80	18.00	33	**1b** (41)
20	DMSO	80	2.50	75	—

[a] The reaction time.
[b] Additional product.

Table 3. The reaction result of hydrazides **2a—c** with tetrazines **1a**,**b** in MeCN in the presence of K_2CO_3 at 80 °C (the molar ratio of reagents 1 : 1 : 1)

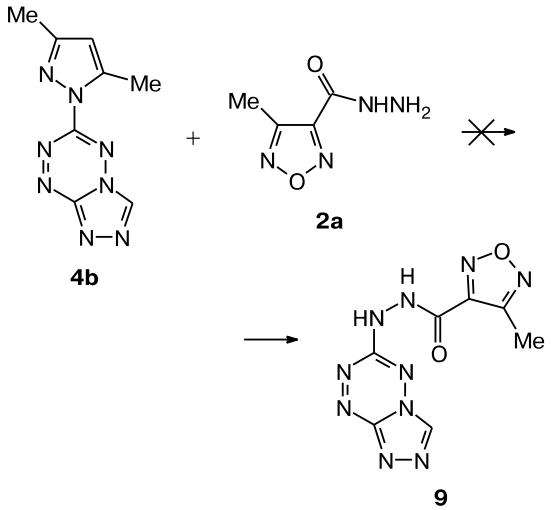
Entry	Tetrazine	Furazan	Reaction time/min	Product (yield (%))
21	**1a**	**2a**	20	**5a** (85)
22	**1a**	**2b**	30	**5b** (87)
23	**1a**	**2c**	10	**5c** (80)
24	**1b**	**2a**	60	**5d** (92)
25	**1b**	**2b**	120	**5e** (90)

We found that the reaction of compounds **1a** and **2a** significantly accelerates in the presence of potassium carbonate (Table 3). Thus, in boiling acetonitrile, where in the absence of K_2CO_3 it required 55 h, in the presence of potassium carbonate it came to completion within 20 min and gave the target product **5a** in good yield (see Table 3, entry *21*). Even poorly soluble in acetonitrile tetrazine **1b** reacts with hydrazide **2a** in the presence of a base to form the corresponding substituted product **5d** within 1 h (see Table 3, entry *24*).

The reaction is of general scope and can be extended to hydrazides of other furazancarboxylic acids (compounds **2b** and **2c**, see Scheme 1, Table 3).

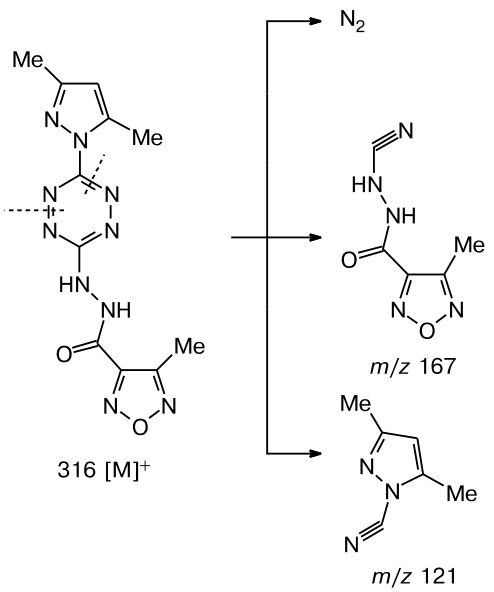
However, it should be noted that attempts to replace the pyrazole fragment in triazolotetrazine **4b** with hydrazide **2a** (Scheme 3) led to a complex mixture of compounds (more than 10 spots on a TLC pattern) in both the presence and the absence of K_2CO_3, from which no target product **9** was isolated. The triazolotetrazine system is known to undergo destruction in the presence of bases.[7]

Scheme 3



The structure of hydrazine disubstituted derivatives **5a—e** was confirmed by the IR, ^1H and ^{13}C NMR spectroscopic data, mass spectrometric data (Table 4), and X-ray diffraction studies of compound **5a**. In the IR spectra, absorption bands of the hydrazine fragment are observed in the region 3208—3232 cm^{-1}, as well as strong absorption bands at ~1710 cm^{-1} characteristic of the C=O bond vibrations. Electron impact produces stable molecular ions, whereas characteristic fragmentation results from desintegration of the tetrazine ring with the concurrent elimination of the N_2 molecules and cleavage of the N—N bond to form ions of two nitriles (Scheme 4).

Scheme 4



The signals observed in the NMR spectra of derivatives **5a—e** agree with the literature data for the structurally similar tetrazine[24,25] and furazan[26—28] derivatives.

The X-ray diffraction data show that the symmetrically independent part of the unit cell contains two molecules of compound **5a** (**A** and **A′**) and three molecules of water (Fig. 1). Each of the structures of symmetrically independent molecules **A** and **A′** is characterized by three planar fragments turned with respect to each other: dimethylpyrazole, methylfurazanylcarbamide, and amino-tetrazinyl. The major difference in the structure of molecules **A** and **A′** is due to the turn of the pyrazole ring with respect to the tetrazine one (the angle is 36.12(7) and 5.78(10)°, respectively) and is apparently determined by the effects of packing of the molecules in the crystal. Despite the difference in the mutual orientation of the pyrazole and tetrazine rings, the bond distances C(5)—N(9) (C(5′)—N(9′)) in molecules **A** and **A′** are equal (1.404(2) and 1.402(2) Å, respectively), that indicates the absence of conjugation between the rings even in molecule **A′**, where these rings are virtually coplanar.

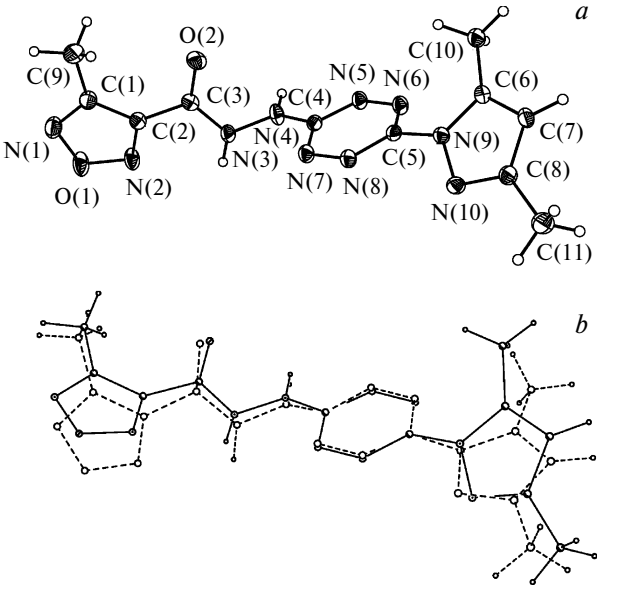


Fig. 1. (*a*) The general view of the symmetrically independent molecule **A** of compound **5a** in representation of atoms as thermal ellipsoids of atomic displacements with 50% probability; (*b*) comparison of conformations of independent molecules **A** (the solid lines) and **A′** (the dashed lines).

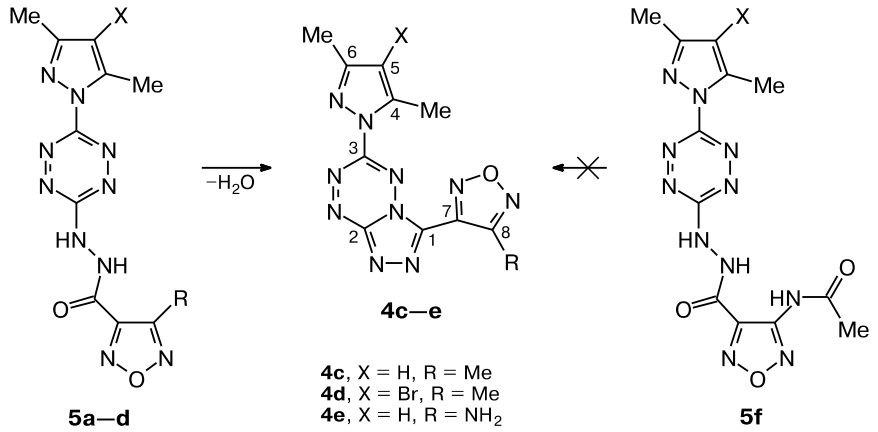
It should be noted that the similar observation has been made earlier[29—32] when the structure of the molecules bearing only dimethylpyrazole and amino-tetrazinyl fragments was studied. The torsional angle C(3)—N(3)—N(4)—C(4) describing a mutual orientation of the methylfurazanylcarbamide and amino-tetrazinyl fragments in molecules **A** and **A′** is 100.0(2) and 119.7(2)°, respectively. Such an orientation is determined by a combined influence of the intramolecular forces and the crystal packing, in which hydrogen bonding is present between the NH protons and the carbonyl groups. The nitrogen atoms of the hydrazine fragment (N(3), N(4) and N(3′), N(4′) in molecules **A** and **A′**, respectively) are characterized by more planar pyramidal geometry (the angles at these atoms are 357.5, 359.7, 358.5, and 359.8° for N(3), N(4), N(3′), and N(4′), respectively), and the lone pair of electrons (LPE) on the atom N(4)—N(4′) is in *trans*-position to the bond N(3)—C(3) (N(3′)—C(3′)) (the torsional angle 167° (148°)), that indicates existence of the anomeric interaction. It should be also noted that the N(3)—N(4) bond is somewhat shorter (1.381(2) and 1.385(2) Å in **A** and **A′**, respectively) as campared to its average value (1.425 Å).[33]

This is apparently caused by participation of the LPE of the atoms N(3) (N(3′)) and N(4) (N(4′)) in the conjugation with the surrounding π-accepting fragments (the tetrazine ring and the carbonyl group), that leads to a lesser repulsion between the "deficient" LPE of the atoms N(3) (N(3′)) and N(4) (N(4′)) and, as a consequence, to the shortening the bond N(3)—N(4).

Table 4. Spectral characteristics of compounds **5a—e**

Compound	^{1}H NMR (DMSO-d_6), δ	^{13}C NMR (DMSO-d_6), δ								MS, *m*/*z*	IR, ν/cm^{-1} (KBr)
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	Other C atoms	
5a	2.21 (s, 3 H, Me); 2.45 (s, 3 H, C(8)Me); 2.53 (s, 3 H, C(6)Me); 6.22 (s, 1 H, C(7)H); 11.02 (br.s, 1 H, NH); 11.65 (br.s, 1 H, NH)	150.9	147.7	158.4	162.1	157.0	141.9	109.4	152.1	8.6 (C(1)Me); 12.7, 13.4 (C(6)Me, C(8)Me)	316 [M]$^+$, 167, 121, 111, 106	3356, 3212, 2932, 1712, 1600, 1568, 1520, 1508, 1500, 1496, 1442,1412, 1276, 1096, 1072, 1036, 964, 912, 892
5b	2.21 (s, 3 H, C(8)Me); 2.48 (s, 3 H, C(6)Me); 6.21 (s, 1 H, C(7)H); 6.48 (s, 2 H, NH_2); 10.94 (br.s, 1 H, NH); 11.57 (br.s, 1 H, NH)	157.9	140.9	158.4	162.1	156.3	141.9	109.3	150.9	12.7, 13.3 (C(6)Me, C(8)Me)	319 [M$^+$+ H_2], 171, 122, 112, 106	3452, 3344, 3212, 2932, 2876, 1708, 1636, 1600, 1564, 1532, 1512, 1496, 1428, 1412, 1324, 1228, 1100, 1068, 968, 1004, 916, 896
5c	2.24 (s, 3 H, C(8)Me); 2.51 (s, 3 H, C(6)Me); 6.23 (s, 1 H, C(7)H); 6.45 (s, 2 H, β-CH, pyrrole); 7.53 (s, 2 H, α-CH, pyrrole); 11.17 (br.s, 1 H, NH); 11.88 (br.s, 1 H, NH)	150.5	142.4	158.5	161.8	156.5	141.9	109.4	150.9	12.7, 13.4 (C(6)Me, C(8)Me); 112.8 (β-CH, pyrrole): 121.3 (α-CH, pyrrole)	367 [M]$^+$, 298, 270, 121, 106	3208, 3084, 2968, 2932, 1712, 1580, 1544, 1484, 1452, 1424, 1276, 1160, 1080, 1046, 1028, 972, 924, 892
5d	2.26 (s, 3 H, Me); 2.48 (s, 3 H, C(8)Me); 2.57 (s, 3 H, C(6)Me); 11.2 (br.s, 1 H, NH); 11.6 (br.s, 1 H, NH)	152.0	147.7	158.1	162.1	156.8	139.7	98.3	149.3	8.6 (C(1)Me); 12.0, 12.3 (C(6)Me, C(8)Me)	396, 394 [M]$^+$, 201, 199, 167, 120, 111	3232, 2980, 2932, 1712, 1700, 1568, 1524, 1492, 1448, 1424, 1404, 1384, 1280, 1220, 1112, 1068, 1060, 1040, 1016, 964, 912, 888
5e	2.25 (s, 3 H, C(8)Me); 2.47 (s, 3 H, C(6)Me); 6.41 (s, 2 H, NH_2); 11.06 (br.s, 1 H, NH); 11.63 (br.s, 1 H, NH)	157.9	139.0	158.2	162.4	156.4	139.8	98.5	149.5	12.1, 12.3 (C(6)Me, C(8)Me)	367 [M$^+$ – NO], 200, 198, 176, 174, 148, 133, 120	3536, 3381, 3311, 3242, 1693, 1646, 1625, 1536, 1489, 1465, 1421, 1277, 1228, 1061, 1015, 962, 840, 793, 737

Scheme 5



Due to the presence in the structure of compound **5a** of the labile NH protons and the oxygen and nitrogen atoms possessing the proton-accepting properties, a wide system of hydrogen bonding is effected in the crystal packing. Due to these hydrogen bonds, molecules are bound in planes parallel to *ab*, which are additionally stabilized by numerous somewhat shortened contacts N...O and N...N, frequently observed in the crystal packings of furazan derivatives.[34—37]

We studied dehydration of the hydrazide fragment in compounds **5** in order to prepare the corresponding triazolo-tetrazines **4** (Scheme 5). Thus, heating of compound **5a** in phosphorus oxychloride in the presence of pyridine leads to a triazole ring closure, and the target derivative **4c** can be isolated in 22% yield. However, like in the synthesis of compound **4a** (see Scheme 1), the dehydration is the most efficient in polyphosphoric acid. In this case, the yield of triazole **4c** increases virtually threefold, reaching 62%. It should be noted that the cyclization takes place only at temperatures above 150 °C; at lower temperatures no annulation of the triazole ring occurs.

Introduction of a bromine atom into the pyrazole ring, apparently, decreases the thermal stability of compounds, and dehydration of compound **5d** in polyphosphoric acid gives rise to the product **4d** in only 30% yield; some resinification is observed in this case.

Compound **5b**, bearing an amino group, in polyphosphoric acid at 150 °C is completely consumed within 15 min. Five minutes after the reaction begins, the TLC data show the presence in the reaction mixture of the product and the starting compound. However, further heating leads to a decrease in the content of both the starting compound and the target product. Compound **4e** was isolated in no more than 2% yield. If the amino group was preliminary acylated, the dehydration of compound **5f** is accompanied by strong resinification: neither the corresponding cyclized product, nor the deacylated product **4e** were isolated.

Thermolysis of compound **5c** in polyphosphoric acid also leads to resinification of the reaction mixture, that can be apparently attributed to the presence of a pyrrole ring in the molecule, which is unstable under such conditions. We unsucceded in isolation of any individual compounds from the reaction mixture.

The structure of obtained triazolotetrazine derivatives **4** was confirmed by the IR, ^{1}H and ^{13}C NMR spectroscopic data, as well as by the mass spectrometric data (Table 5).

Table 5. Spectral characteristics of compounds **4a—e**

Compound	^{1}H NMR, δ	^{13}C NMR, δ							MS, *m/z*	IR, ν/cm^{-1}
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	Other C atoms		
4a	2.34 (s, 3 H, C(6)Me); 2.62 (s, 3 H, C(4)Me); 6.46 (s, 1 H, C(5)H)	135.9 (q, $^2J_{CF}$ = = 42.5 Hz)	150.8	150.5	144.1	112.2	154.2	13.5, 13.6 (C(4)Me, C(6)Me); 117.7 (q, (CF_3, $^1J_{C,F}$ = 271.2 Hz)	284 [M]$^+$, 265, 187, 161, 121, 107	2937, 1591, 1542, 1526, 1462, 1405, 1372, 1294, 1250, 1211, 1168, 1106, 1043, 1021, 966, 820

(*to be continued*)

Table 5 (*continued*)

Compound	^{1}H NMR, δ	^{13}C NMR, δ							MS, *m/z*	IR, ν/cm^{-1}
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	Other C atoms		
4b	2.22 (s, 3 H, C(6)Me); 2.62 (s, 3 H, C(4)Me); 6.45 (s, 1 H, C(5)H); 12.23 (s, 1 H, C(1)H)	137.8	150.9	150.7	143.7	111.2	152.9	13.3, 13.6 (C(6)Me, C(8)Me)	—	3084, 1586, 1525, 1470, 1415, 1404, 1359, 1282, 1144, 1109, 1072, 1027, 1012, 974, 946, 838
4c	2.32 (s, 3 H, C(8)Me); 2.67 (s, 3 H, C(6)Me); 2.84 (s, 3 H, C(4)Me); 6.43 (s, 1 H, C(5)H)	136.6	150.8	150.7	142.7	111.7	153.6	9.5 (C(8)Me); 13.5, 13.7 (C(4)Me, C(6)Me); 143.9 (C(7)); 151.9 (C(8))	298 [M]$^+$, 213, 158, 121, 106, 95	1584, 1536, 1472, 1396, 1288, 1236, 1112, 1044, 1016, 996, 984, 968, 892
4d	2.36 (s, 3 H, C(8)Me); 2.69 (s, 3 H, C(6)Me); 2.89 (s, 3 H, C(4)Me);	137.4	151.5	150.9	141.9	101.8	152.6	10.1 (C(8)Me); 13.0, 13.5 (C(6)Me, C(4)Me); 143.2 (C(7)); 152.5 (C(8))	—	2931, 1576, 1534, 1473, 1395, 1358, 1296, 1240, 1043, 1017, 997, 982, 895
4e	2.68 (s, 3 H, C(6)Me); 2.87 (s, 3 H, C(4)Me); 6.42 (s, 1 H, C(7)H); 6.48 (s, 2 H, NH_2)	—	—	—	—	—	—	—	299 [M]$^+$, 214, 121, 106	—

The signals in the ^{13}C NMR spectra were assign based on the selective heteronuclear double resonance ^{1}H—^{13}C and ^{1}H—^{15}N HMBC, as well as based on the data on the related compounds.[24,25]

In conclusion, it was shown that furazancarboxylic hydrazides can serve as nucleophiles and substitute for the dimethylpyrazole fragment bonded to the *s*-tetrazine ring. The success of thermal dehydration of 1-acyl-2-tetrazinylhydrazines in polyphosphoric acid to form the corresponding [1,2,4]triazolo[4,3-*b*]-*s*-tetrazines depends on the type of substituents on the molecule. Our work results in the synthesis of the first representatives of [1,2,4]triazolo[4,3-*b*]-*s*-tetrazines containing an electron-withdrawing group (CF_3 group or furazanyl fragment) as a substituent on the triazole ring.

Experimental

Melting points were measured on a Gallenkamp melting point apparatus and were not corrected. ^{1}H, ^{13}C, ^{15}N, and ^{19}F NMR spectra on the natural content of isotopes were recorded on a Bruker AM-300 spectrometer (300.13, 75.7, 30.4, and 282.4 MHz, respectively) in DMSO-d_6 or $CDCl_3$. Chemical shifts ^{15}N were measured relative to the external standard $MeNO_2$. 2D spectra were recorded on a Bruker Avance 600 spectrometer using a Bruker standard procedure. The HMBC experiments were optimized for the spin-spin coupling constants J_{H-C} and J_{H-N} equal to 8 Hz. Mass spectra were recorded on Varian MAT CH-6 and Varian MAT CH-111 (70 eV) instruments. IR spectra were recorded on a Bruker Alpha-T spectrometer (KBr pellets). Reaction progress and products purity were monitored by TLC on Sorbfil precoated plates, SiO_2 40/100 silica gel was used for preparative chromatography. The starting 3-R-4-furazancarboxylic hydrazides **2** were obtained according to the procedures described earlier.[22,38] Solvents were dried according to the standard procedures. Polyphosphoric acid was purchased from Lancaster.

X-ray diffraction studies. Single crystals of compound **5a** suitable for X-ray diffraction experiment were obtained by slow concentration of its solution in aqueous isopropanol. Crystals of **5a** ($C_{11}H_{12}N_{10}O_2 \cdot 1.5H_2O$) at 100 K are monoclinic, $a = 8.928(2)$ Å, $b = 11.774(3)$ Å, $c = 29.879(7)$ Å, $\beta = 92.496(4)°$, $V = 3138.1(12)$ Å^3, $Z = 8$, space group $P2_1/n$, $\mu = 0.114$ mm^{-1}, $d_{calc} = 1.453$ g cm^{-3}. Intensities of 38951 reflections were measured on a SMART APEX2 CCD diffractometer (λ(Mo-Kα) = 0.71073 Å, graphite monochromator, ω-scan technique, 2θ□< 60°). The starting array of measured intensities was processed using the SAINT and SADABS program, included into the APEX2 program package.[39] The structure was solved by direct method and refined by full-matrix least squares method in anisotropic approximation for nonhydrogen atoms on F^2_{hkl}. Hydrogen atoms were placed into geometrically calculated positions except for the hydrogen atoms of amino groups, whose positions were localized from the

differential syntheses of electron density and then normalized on the distance of 0.90 Å. All the hydrogen atoms were refined using the riding model ($U_{iso}(H) = nU_{eq}(s,N)$, where $n = 1.5$ for the carbon atoms of methyl groups, $n = 1.2$ for the N atoms). The refinement included 9138 independent reflections ($R_{int} = 0.0609$), number of refined parameters was 448. Convergence of refinement for all the independent reflections $wR_2 = 0.1115$, GOOF = 1.014 ($R_1 = 0.0478$ on 6163 reflections with $I > 2\sigma(I)$). All the calculations were performed on IBM PC AT using the SHELXTL program package.[40] The structure was deposited with the Cambridge Structural Database (CCDC 852363).

Preparation of *N*′-[6-(3,5-dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-methylfurazan-3-carbohydrazide 5a in different solvents (general procedure). A mixture of tetrazine **1a** (0.27 g, 0.1 mmol) and hydrazide **2a** (0.14 g, 0.1 mmol) in the corresponding solvent 10 mL) was stirred on heating until the reaction reached completion (TLC monitoring, eluent CCl_4—MeCN (3 : 1)). The method for the isolation of product **5a** depends on the type of solvent used. For the reaction conditions and the product yields, see Table 1. The data for compound **5a** are summarized in Table 4.

A. When the reaction was carried out in alcohols and DMF, formation of two product was observed. The starting compounds and the reaction products are well detectable by TLC: $R_f(\mathbf{8}) > R_f(\mathbf{1}) > R_f(\mathbf{2}) > R_f(\mathbf{5})$. The reaction mixture was cooled to ~20 °C and diluted with water (10 mL). An orange precipitate formed was filtered off, washed with hexane (15 mL), and recrystallized from the $Pr^iOH—H_2O$ (1 : 1) mixture. The filtrate was extracted with hexane (30 mL), the solvent was evaporated to obtain a mixture of tetrazine **8a**—**d** and 3,5-dimethylpyrazole, which was separated by column chromatography on SiO_2 (eluent dichloromethane).

3-(3,5-Dimethylpyrazol-1-yl)-6-methoxy-*s*-tetrazine (8a). The yield was 29%, pink solid compound, m.p. 157—158 °C (*cf.* Ref. 4, m.p. 156—157 °C). Found (%): C, 46.67; H, 4.93, N, 40.71. $C_8H_{10}N_6O$ (M = 206.20). Calculated (%): C, 46.60, H, 4.89, N, 40.76. MS, *m/z*: 206 $[M]^+$ 121, 106, 94, 80, 67. IR, ν_{max}/cm^{-1}: 3112, 3024, 2960, 2924, 1644, 1576, 1484, 1448, 1400, 1376, 1356, 1280, 1160, 1136, 1084, 1048, 1028, 1000, 972, 952, 824, 760, 680, 588, 572. ^{1}H NMR (DMSO-d_6), δ: 2.25 (s, 3 H, Me, C(3)); 2.50 (s, 3 H, Me, C(5)); 4.27 (s, 3 H, OMe); 6.29 (s, 1 H, H, C(4)). ^{13}C NMR (DMSO-d_6), δ: 166.1 (C(1)); 158.8 (C(2)); 151.5 (C(5)); 142.4 (C(3)); 110.1 (C(4)); 56.78 (OMe); 13.0, 13.3 (C(5)Me; C(3)Me). ^{15}N NMR (DMSO-d_6), δ: 293.1, 301.6, 353.5, 373.2.

3-(3,5-Dimethylpyrazol-1-yl)-6-ethoxy-*s*-tetrazine (8b). The yield was 20%, pink amorphous compound, m.p. 114—115 °C. Found (%): C, 49.13; H, 5.55, N, 38.08. $C_9H_{12}N_6O$ (M = 220.23). Calculated (%): C, 49.08: H, 5.49: N, 38.16. MS, *m/z*: 220 $[M]^+$ 121, 106, 94, 80. IR, ν_{max}/cm^{-1}: 3104, 2988, 2964, 2932, 1576, 1484, 1432, 1388, 1348, 1328, 1280, 1112, 1088, 1024, 988, 968, 952, 932, 828, 764, 660. ^{1}H NMR (DMSO-d_6), δ: 1.49 (t, 3 H, $CH_2C\underline{H}_3$, J = 7 Hz); 2.25 (s, 3 H, C(3)Me); 2.50 (s, 3 H, C(5)Me); 4.65 (q, 2 H, $C\underline{H}_2Me$, J = 7 Hz); 6.28 (s, 1 H, C(4)H). ^{13}C NMR (DMSO-d_6), δ: 165.7 (C(1)); 158.7 (C(2)); 151.5 (C(5)); 142.3 (C(3)); 110.0 (C(4)); 65.8 ($O\underline{C}H_2Me$); 14.13 ($OCH_2\underline{C}H_3$); 13.4, 13.0 (C(3)Me; C(5)Me).

3-(3,5-Dimethylpyrazol-1-yl)-6-(*iso*-propoxy)-*s*-tetrazine (8c). The yield was 5%, light pink amorphous compound, m.p. 47—48 °C. Found (%): C, 51.36; H, 6.07; N, 35.80. $C_{10}H_{14}N_6O$ (M = 234.26). Calculated (%): C, 51.29; H, 6.02; N, 35.88. MS, *m/z*: 234 $[M]^+$ 121, 106. IR, ν_{max}/cm^{-1}: 2976, 2928, 1576, 1476, 1388, 1312, 1148, 1104, 1084, 1044, 1024, 984, 952, 932, 820, 760, 704. ^{1}H NMR (DMSO-d_6), δ: 1.49 (d, 6 H, $CH\underline{Me}_2$, J = 6.1 Hz); 2.25 (s, 3 H, C(3)Me); 2.51 (s, 3 H, C(5)Me); 5.47 (septet, 1 H, $C\underline{H}Me_2$, J = 6.1 Hz); 6.26 (s, 1 H, C(4)H). ^{13}C NMR (DMSO-d_6), δ: 165.3 (C(1)); 158.5 (C(2)); 151.3 (C(5)); 142.2 (C(3)); 109.8 (C(4)); 73.56 ($\underline{C}HMe_2$); 21.3 ($CH\underline{Me}_2$); 13.2, 12.9 (C(3)Me; C(5)Me).

3-(3,5-Dimethylpyrazol-1-yl)-6-(*N*,*N*-dimethylamino)-*s*-tetrazine (8d). The yield was 10%, red finely crystalline compound, m.p. 141—142 °C (*cf.* Ref. 4: m.p. 137—138 °C). Found (%): C, 49.37; H, 6.00; N, 44.66. $C_9H_{13}N_7$ (M = 219.25). Calculated (%): C, 49.30; H, 5.98; N, 44.72. MS, *m/z*: 219 $[M]^+$, 122, 106. IR, ν_{max}/cm^{-1}: 3146, 3101, 2922, 2871, 2798, 1573, 1488, 1411, 1399, 1368, 1296, 1207, 1131, 1076, 1038, 1021, 974, 948, 845, 810, 755, 611, 576, 531. ^{1}H NMR ($CDCl_3$), δ: 2.25 (s, 3 H, C(3)Me); 2.46 (s, 3 H, C(5)Me); 3.30 (s, 6 H, NMe_2); 6.02 (s, 1 H, C(4)H). ^{13}C NMR ($CDCl_3$), δ: 156.2 (C(1)); 151.2 (C(5)); 143.9 (C(2)); 141.5 (C(3)); 104.1 (C(4)); 36.7 (NMe_2); 8.5, 8.1 (C(3)Me, C(5)Me).

B. When the reaction was carried out in THF, nitromethane, benzene, or dioxane, no formation of side products was observed. After the reaction was completed, the solvent was evaporated to dryness, and the residue was recrystallized from $Pr^iOH—H_2O$ (1 : 1).

C. When the reaction was carried out in glyme or DMSO (the reaction mixture was diluted with water (10 mL)), an orange precipitate formed was filtered off, washed with water (2×3 mL), and recrystallized from $Pr^iOH—H_2O$ (1 : 1).

D. After reflux in chloroform for 54 h, the reaction mixture still contained about half of unreacted starting compounds. The reaction mixture was cooled to ~20 °C, a formed precipitate of product **5a** was filtered off and recrystallized. The filtrate containing the starting compounds **1a** and **2a** was concentrated to dryness. The residue was dissolved in hot EtOH (2 mL), the solution was cooled to −5 °C; a white precipitate formed was filtered off to obtain methylfurazancarboxylic hydrazide **2a**. The filtrate was concentrated to dryness, and the residue was recrystallized from $Pr^iOH—H_2O$ (7 : 1) to yield the starting tetrazine **1a**.

E. When the reaction was carried out in water, it was stopped after heating tetrazine **1a** and hydrazide **2a** for 55 h at 80 °C (according to the TLC data, the reaction mixture still contained much of the starting compounds). The mixture was cooled to ~20 °C, the poorly soluble in water compounds **1a** and **2a** were filtered off, the aqueous filtrate was extracted with dichloromethane (10 mL), whose concentration gave product **5a**. The aqueous solution after acidification with 1% HCl (3 mL) and extraction with diethyl ether (2×10 mL) furnished **3-(3,5-dimethylpyrazol-1-yl)-6-hydroxy-*s*-tetrazine (8e)**, the yield was 11%, dark red solid compound, m.p. 205 °C (with decomp.). Found (%): C, 43.82; H, 4.16; N, 43.67. $C_7H_8N_6O$ (M = 192.18). Calculated (%): C, 43.75; H, 4.20; N, 43.73. IR, ν_{max}/cm^{-1}: 3136, 3088, 3036, 2900, 1744, 1708, 1692, 1552, 1508, 1432, 1404, 1372, 1264, 1160, 1140, 1104, 1064, 1024, 992, 976, 836, 808, 780, 764. ^{1}H NMR (DMSO-d_6), δ: 2.25 (s, 3 H, C(3)Me); 2.39 (s, 3 H, C(5)Me); 6.20 (s, 1 H, C(4)H). ^{13}C NMR (DMSO-d_6), δ: 152.0 (C(1)); 150.6 (C(5)); 147.7 (C(2)); 141.9 (C(3)); 108.8 (C(4)); 13.21 12.11 (C(3)Me; C(5)Me).

F. When the reaction was carried out in ionic liquid, a mixture of [emim][BF_4] (3 mL), tetrazine **1a** (0.1 g, 0.37 mmol), and hydrazide **2a** (0.05 g, 0.37 mmol) was heated for 24 h at

80 °C. Then the reaction mixture was cooled to 30 °C and diluted with water (20 mL). The product **5a** was extracted with diethyl ether (2×50 mL), the extract was dried with magnesium sulfate, concentrated, and the residue was recrystallized from $Pr^iOH—H_2O$ (1 : 1).

3,6-Bis(4-bromo-3,5-dimethylpyrazol-1-yl)-*s*-tetrazine (1b). *N*-Bromosuccinimide (1.95 g, 11 mmol) was added to a solution of tetrazine **1a** (1.47 g, 5.5 mmol) in hot MeCN (20 mL). The reaction mixture was refluxed for 2 min, then cooled to ~20 °C. A precipitate formed was filtered off and washed with MeCN (10 mL) to obtain a reddish orange amorphous compound (2.11 g, 91%) , m.p. 262—263 °C (*cf.* Ref. 4: m.p. 262 °C). MS, *m/z*: 428 $[M]^+$, 199, 120, 105. IR, ν_{max}/cm^{-1}: 1568, 1500, 1456, 1428, 1404, 1388, 1056, 1008, 936, 780. ^1H NMR ($CDCl_3$), δ: 2.39 (s, 3 H); 2.72 (s, 3 H). ^{13}C NMR ($CDCl_3$), δ: 159.1 (C(1)); 153.4 (C(5)); 141.1 (C(3)); 102.5 (CBr); 13.8, 12.8.

***N′*-[6-(4-Bromo-3,5-dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-methylfurazan-3-carbohydrazide (5d).** A mixture of tetrazine **1b** (0.27 g, 0.1 mmol) and hydrazide **2a** (0.14 g, 0.1 mmol) in the corresponding solvent (10 mL) was heated with stirring until the reaction reached completion (TLC monitoring, eluent CCl_4—MeCN (3 : 1)). For the reaction conditions and the product yields, see Table 2.

A (Carrying out the reaction in alcohols). The starting compounds were dissolved in alcohol on heating. The reaction progress was monitored by TLC (eluent CCl_4—MeCN (3 : 1)). After the reaction reached completion, formation of two products, **5d** (R_f = 0.4) and **8f** (R_f = 0.9), was observed. The reaction mixture was cooled to ~20 °C and diluted with water (10 mL). A precipitate formed was filtered off and washed with hexane to obtain product **5d** (0.08 g, 67%) as an orange amorphous powder, m.p. 186—189 °C (see also Table 4). The filtrate was extracted with hexane, the solvent was evaporated to yield a mixture of 3-(4-bromo-3,5-dimethylpyrazol-1-yl)-6-(3-ethoxy)-1,2,4,5-tetrazine (**8f**) and 4-bromo-3,5-dimethylpyrazole, which was separated by column chromatography on SiO_2 (eluent hexane), R_f = 0.8, R_f = 0, respectively.

3-(4-Bromo-3,5-dimethylpyrazol-1-yl)-6-ethoxy-*s*-tetrazine (8f). The yield was 30%, pink amorphous compound, m.p. 100—102 °C. Found (%): C, 36.16; H, 3.75; N, 28.04. $C_9H_{11}N_6OBr$ (*M* = 299.13). Calculated (%): C, 36.14; H, 3.71; N, 28.10. MS, *m/z*: 298 and 300 $[M]^+$, 199, 120, 105. IR, ν_{max}/cm^{-1}: 2924, 2852, 1568, 1493, 1454, 1389, 1348, 1064, 1034, 961, 925, 789, 696, 657, 620, 588, 552. ^1H NMR (DMSO-d_6), δ: 1.50 (t, 3 H, $CH_2C\underline{H}_3$, *J* = 7 Hz); 2.28 (s, 3 H, C(3)Me); 2.51 (s, 3 H, C(5)Me); 4.70 (q, 2 H, $C\underline{H}_2Me$, *J* = 7 Hz). ^{13}C NMR (DMSO-d_6), δ: 165.9 (C(1)); 158.4 (C(2)); 150.0 (C(5)); 140.1 (C(3)); 99.1 (C(4)); 66.0 ($O\underline{C}H_2Me$); 14.1, 14.0 (C(3)Me; C(5)Me); 12.3 ($OCH_2\underline{C}H_3$).

B. When the reaction was carried out in DMSO, the reaction mixture was diluted with water (10 mL), an orange precipitate formed was filtered off, washed with water (2×3 mL), and recrystallized from $Pr^iOH—H_2O$ (1 : 1).

C. When the reaction was carried out in acetonitrile or glyme, tetrazine **1b** and hydrazide **2a** were heated at 80 °C for 25 h (TLC showed that the mixture still contained the starting compounds). The reaction mixture was cooled to ~20 °C, a poorly soluble tetrazine **1b** was filtered off. The filtrate was diluted with water (10 mL) and extracted with dichloromethanene, the extract was dried with $MgSO_4$ and concentrated to obtain product **5d**.

D. After reflux in chloroform for 54 h, the mixture still contained about half of the starting compounds. The reaction mixture was cooled to ~20 °C, a formed precipitate of product **5d** was filtered off and recrystallized. The filtrate containing the starting compounds **1b** and **2a** was concentrated to dryness. The residue was recrystallized from aqueous ethanol (2 mL) to yield the starting tetrazine **1b**.

Synthesis of compounds 5 in the presence of potassium carbonate (general procedure). Potassium carbonate (1 mmol) was added to a solution of 3,6-bis(4-X-3,5-dimethylpyrazol-1-yl)-*s*-tetrazine (**1a** or **1b**) (1 mmol) and 3-R-4-furazancarboxylic hydrazide **2a**—**c** (1 mmol) in anhydrous acetonitrile (10 mL). A dark claret-colored suspension formed was refluxed until the reaction reached completion (TLC monitoring, eluent CCl_4—MeCN (1 : 1)). The reaction mixture was cooled to ~20 °C and diluted with water (10 mL) to obtain a homogeneous solution. This solution was neutralized with 3% aqueous HCl to pH 3, with the color changing from dark brown to orange and a precipitate forming. The product was filtered off, washed with water (2×5 mL), dried in air, and recrystallized from 50% aq. Pr^iOH. The reaction time and the product yields are summarized in Table 3.

***N′*-[6-(3,5-Dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-methylfurazan-3-carbohydrazide (5a)**, orange amorphous powder, m.p. 193—194 °C ($Pr^iOH—H_2O$).

***N′*-[6-(3,5-Dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-aminofurazan-3-carbohydrazide (5b)**, orange amorphous powder, m.p. 257—258 °C (Pr^iOH).

***N′*-[6-(3,5-Dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-(pyrrol-1-yl)furazan-3-carbohydrazide (5c)**, orange amorphous powder, m.p. 228—229 °C ($Pr^iOH—H_2O$).

***N′*-[6-(4-Bromo-3,5-dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-methylfurazan-3-carbohydrazide (5d)**, orange amorphous powder, m.p. 189—192 °C ($Pr^iOH—H_2O$).

***N′*-[6-(4-Bromo-3,5-dimethylpyrazol-1-yl)-*s*-tetrazin-3-yl]-4-aminofurazan-3-carbohydrazide (5e)**, orange amorphous powder, m.p. 238—239 °C (Pr^iOH).

Cyclization of hydrazinotetrazine acyl derivatives **(general procedure).** A suspension of hydrazinotetrazine **5a** (0.16 g, 0.5 mmol) in polyphosphoric acid (0.8 g) was heated with stirring to 150 °C. The solution formed was stirred at 150 °C for 5 min. Then the reaction mixture was cooled to 100 °C and poured into water. A precipitate was filtered off, washed with water, and recrystallized. Spectral characteristics of compounds **4a**—**c** are given in Table 5.

6-(3,5-Dimethylpyrazol-1-yl)-3-trifluoromethyl-1,2,4-triazolo[4,3-*b*]-*s*-tetrazine (4a). The yield was 56%, yellow amorphous powder, m.p. 193—194 °C ($Pr^iOH—H_2O$). ^{19}F NMR (DMSO-d_6), δ: −63.6 (CF_3). ^{15}N NMR (DMSO-d_6), δ: −179 (C(4)N), −79 (C(6)N). Found (%): C, 38.00; H, 2.41; N, 39.34. $C_9H_7F_3N_6$ (*M* = 284.20). Calculated (%): C, 38.04; H, 2.48; N, 39.43.

6-(3,5-Dimethylpyrazol-1-yl)-3-(3-methylfurazan-4-yl)-1,2,4-triazolo-[4,3-*b*]-*s*-tetrazine (4c). The yield was 57%, yellow amorphous powder, m.p. 165—170 °C ($EtOH—H_2O$). Found (%): C, 44.23; H, 3.43; N, 46.88. $C_{11}H_{10}N_{10}O$ (*M* = = 298.26). Calculated (%): C, 44.30; H, 3.38; N, 46.96.

6-(4-Bromo-3,5-dimethylpyrazol-1-yl)-3-(3-methylfurazan-4-yl)-1,2,4-triazolo-[4,3-*b*]-*s*-tetrazine (4d). The yield was 30%, yellow amorphous powder, m.p. 183—184 °C (EtOH). ^{15}N NMR (DMSO-d_6), δ: −176.9, −176.6, −130.7, −78.3, −56.1, −39.5,

30.1, 35.3, 36.0, 59.5. Found (%): C, 35.12; H, 2.47; N, 37.02. $C_{11}H_9BrN_{10}O$ (M = 377.16). Calculated (%): C, 35.03; H, 2.41; N, 37.14.

The authors are grateful to A. S. Shashkov for recording and discussion of 2D NMR spectra.

This work was partially financially supported by the Division of Chemistry and Material Sciences of the Russian Academy of Sciences (Programs OKhNM-04 and PRAN-7), as well as the Russian Foundation for Basic Research (Project No. 09-03-12230).

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Received May 17, 2011;
in revised form November 17, 2011