Synthesis of secondary and tertiary aminofurazans

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Reactions of nitrofurazans with primary and secondary amines were studied. Conditions were found which allow the efficient replacement of the nitro group with these nucleophiles. Transformations of the amidoxime fragment, which is bound to the furazan ring and contains an amino substituent, enable one to substantially expand the spectrum of polyfunctional derivatives. The structures of the amines synthesized were studied by X-ray diffraction analysis.

Key words: nitrofurazans, aminofurazans, amidoximes, nucleophilic substitution, NMR study, X-ray diffraction analysis.

The electron-withdrawing character of the furazan ring hinders direct alkylation of aminofurazans. Only 3,4-diaminofurazan containing two electron-donating substituents was successfully subjected to alkylation. Its treatment with alkyl bromides under phase-transfer catalysis conditions afforded a mixture of di-, tri-, and tetraalkylation products.[1] Main procedures for the preparation of *N*-alkyl- and *N*-arylaminofurazans are based on dehydration of the corresponding *N*-substituted aminoglyoximes or reduction of acylaminofurazans. Both these procedures are laborious and, as a rule, afford target amines in low yields. Moreover, these procedures allow one to synthesize compounds with only a very limited combination of substituents. The syntheses, properties, and fields of application of aminofurazans were surveyed in reviews.[2—4]

In continuation of our studies aimed at developing efficient methods for the synthesis of furazan derivatives with various combinations of substituents, we investigated routes to secondary and tertiary amines of the furazan series, because these derivatives are of most interest from a pharmacological standpoint.

Earlier,[5] we have demonstrated that ammonia readily replaces the nitro group in 3,4-dinitrofurazan (**1**) in anhydrous $CHCl_3$ at −10 °C. The nitro group in 3,4-dinitrofuroxan is replaced even more readily upon treatment with ammonia or alkylamines in a medium of CH_2Cl_2, $CHCl_3$, or CCl_4 at a temperature from −15 to −20 °C.[6—8] However, methylamine, which is more nucleophilic than ammonia, does not react with dinitro compound **1** under anhydrous conditions in the above-mentioned solvents as well as in MeCN. To the contrary, the reaction of a chloroform solution of compound **1** with an aqueous solution of methylamine (a two-phase system) occurs almost instantly to form monosubstitution product **2** in 85% yield (Scheme 1). It should be noted that *C*-substituted derivatives of methylamine react with compound **1** both under anhydrous conditions and in an organic solvent—water system. In these reactions, one nitro group is selectively replaced under mild conditions. The nitrite ion generated in the course of the reaction reacts with the starting amine to give the corresponding alcohol (GLC data). The nucleophilicity of the latter is much lower than that of amine. Hence, this side process can be ignored but only if an excess of amine can be used (method *A*; more than two moles of amine per nitro group). However, it is unreasonable to use this approach in the case of expensive amines. Deactivation of the nitrite ion is also of considerable importance in the reactions of compound **1** with diamines. To find conditions, under which the target product can be prepared with the use of only one mole of amine, we examined the reaction of compound **1** with benzylamine as a model process. We used various additives, which can bind the nitrite ion. A two-phase CH_2Cl_2—H_2O system in the presence of bases appeared to be most efficient (Table 1). Additives, both reducing the nitrite ion (urea or NH_2SO_3H)

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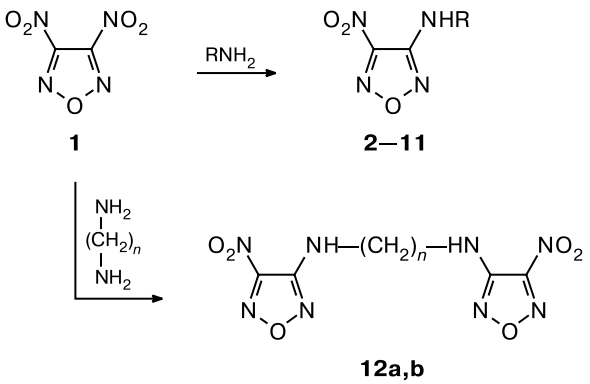
Table 1. Influence of the reaction conditions on the yield of product **3** in the reaction of compound **1** with $BnNH_2$ (molar ratio of 1 : 1)

Solvent	Additive (equiv.)	*T*/°C	τ/h	Yield of **3** (%)
MeCN	Et_3N (1.2)	0→20	0.5	41
$MeO(CH_2)_2OMe$	Et_3N (1.2)	0→20	0.5	44
CH_2Cl_2 (method *B*)	Et_3N (1.2)	0→20	0.5	47
CH_2Cl_2	Et_3N (1.2) + + $OC(NH_2)_2$ (1.2)	0→20	0.5	61
CH_2Cl_2—H_2O (1 : 1)	Et_3N (1.2) + + $OC(NH_2)_2 \cdot H_2O_2$ (1.2)	0→20	1	53
CH_2Cl_2—H_2O (1 : 1)	Et_3N (1.2) + + $OC(NH_2)_2$ (1.2)	0→20	1	53
$CHCl_3$	NH_2SO_3H (1) + + Et_3N (2.1)	0→20	1	65
$MeO(CH_2)_2OMe$	LiOH (1)	−10→20	3	13
CH_2Cl_2—H_2O (1 : 1)	Na_2CO_3 (1)	0→20	3	68
CH_2Cl_2—H_2O (1 : 1) (method *C*)	$NaHCO_3$ (2)	0→20	3	70
CH_2Cl_2—H_2O (1 : 1) (method *D*)	Na_2CO_3 (1) + + $Na_2S_2O_8$ (0.5)	0→20	2	76
CH_2Cl_2—H_2O (1 : 1)	Et_3N (0.5) + Na_2CO_3 (1) + + $Na_2S_2O_8$ (0.5)	0→20	2	83

and oxidizing this ion to nonnucleophilic nitrate ($OC(NH_2)_2 \cdot H_2O_2$ or $Na_2S_2O_8$), also increase the yield of amine **3**.

Scheme 1

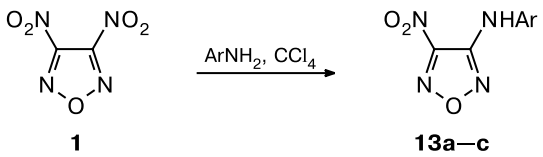


n = 2 (**12a**), 5 (**12b**)

A series of primary mono- and diamines were introduced into the reaction with compound **1**. The synthesis was carried using the above-mentioned methods *A*, *B*, and *C* (see Scheme 1 and Table 2). The application of these methods to the synthesis of functionalized amines not necessarily gives analogous results (see Table 2). For example, reactions under the conditions, which are most efficient in the reactions with benzylamine, sometimes produce the worst results. It is known that many primary amines are accessible as salts. The method *C* is most convenient for reactions with their use. This method does not require preisolation of a pure base. The reaction proceeds smoothly in the presence of a proportional amount of sodium bicarbonate neutralizing acid.

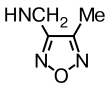
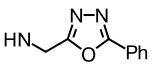
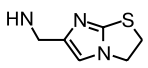
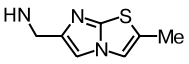
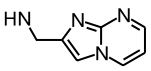
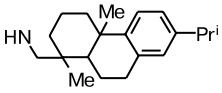
Upon mixing of nitrofurazans with aniline, isomeric toluidines, or naphthylamines, the reaction mixture developed an intense color. The nitro group eliminated from the furazan ring acts as a diazotizating agent with respect to these arylamines, and the subsequent azo-coupling reactions give rise to azo dyes as by-products. The TLC analysis of these mixtures revealed the presence of a chain of intensely colored spots. The use of various additives analogous to those listed in Table 1 did not lead to substantial suppression of side processes. Individual (arylamino)furazans were isolated only in rare cases. However, it appeared that treatment of dinitrofurazan **1** with a threefold excess of arylamines on cooling in a solution in CCl_4 afforded products **13a—c** (Scheme 2, see Table 2).

Scheme 2



Ar = 3-MeC_6H_4 (**a**), 4-MeC_6H_4 (**b**), 1-naphthyl (**c**)

Table 2. Physicochemical characteristics of secondary 3-(R-amino)-4-nitrofurazans **2—13**

Compound	NHR	Yield (%) (method)	M.p./°C	Found / Calculated (%)			Molecular formula	Molecular weight
				C	H	N		
2	NHMe	0 (*A*, *B*) 73 (*C*) 85*	30—32 (CCl_4)	25.06 25.01	2.83 2.80	38.79 38.88	$C_3H_4N_4O_3$	144.09
3	$NHCH_2Ph$	59 (*A*) 47 (*B*) 70 (*C*) 76 (*D*)	69—70 (hexane)	49.10 49.08	3.69 3.66	25.39 25.45	$C_9H_8N_4O_3$	220.06
4		75 (*A*) 68 (*B*) 76 (*C*) 64 (*D*)	62—64 (hexane)	31.91 31.85	2.69 2.62	37.03 37.17	$C_6H_6N_6O_4$	226.05
5		52 (*B*) 45 (*C*) 28 (*D*)	148—150 (CCl_4)	45.89 45.82	2.92 2.80	29.11 29.17	$C_{11}H_8N_6O_4$	288.06
6		68 (*B*) 67 (*C*)	163—165 ($CHCl_3$)	35.89 35.82	3.10 3.01	31.27 31.35	$C_8H_8N_6O_3S$	268.04
7		70 (*B*) 53 (*C*) 82 (*D*)	206—208 (CCl_4—CH_2Cl_2)	38.66 38.57	2.99 2.89	29.89 30.00	$C_9H_8N_6O_3S_1$	280.04
8		75 (*B*) 43 (*C*) 59 (*D*)	192—193 (CCl_4—CH_2Cl_2)	41.46 41.37	2.81 2.70	37.48 37.55	$C_9H_7N_7O_3$	261.06
9		52 (*C*)	23—25 (MeOH)	47.50 47.43	5.99 5.97	27.61 27.65	$C_{10}H_{15}N_5O_3$	253.26
10		41 (*B*) 40 (*C*)	Oil	66.54 66.46	7.41 7.36	14.05 14.10	$C_{22}H_{29}N_4O_3$	397.22
11	NHAd	72 (*A*) 61 (*B*) 58 (*C*)	95—102 (MeOH)	54.62 54.52	6.19 6.11	21.15 21.21	$C_{12}H_{16}N_4O_3$	264.12
12a	$NH(CH_2)_2NH$	77 (*C*)	161—164 (CCl_4—CH_2Cl_2)	25.26 25.17	2.15 2.11	39.09 39.16	$C_6H_6N_8O_6$	286.04
12b	$NH(CH_2)_5NH$	86 (*C*)	61—64 (CCl_4)	33.02 32.92	3.76 3.69	34.09 34.14	$C_9H_{12}N_8O_6$	328.09
13a	3-MeC_6H_4NH	73	141—142 (pentane)	49.13 49.09	3.74 3.66	25.38 25.45	$C_9H_8N_4O_3$	220.19
13b	4-MeC_6H_4NH	67.9	175—176 (CCl_4)	49.15 49.09	3.69 3.66	25.40 25.45	$C_9H_8N_4O_3$	220.19
13c	(1-Naphthyl)-NH	56.7	141—142 (Pr^iOH)	56.33 56.25	3.21 3.15	21.79 21.87	$C_{12}H_8N_4O_3$	256.22

* Treatment of a solution of compound **1** with a fivefold excess of an aqueous $MeNH_2$ solution.

Low solubility of products **13a—c** in CCl_4 hinders their involvement in side azo-coupling reactions.

Heating of a mixture of compound **1** with 3,4-diaminofurazan (**14**) in MeCN gave rise to triazene **15** in 15—25% yield (Scheme 3). In the presence of bases (Et_3N, Py, or Na_2CO_3), compound **1** decomposed and amine **14** was quantitatively recovered from the reaction mixture. Treatment of amine **14** with Bu^nLi in a solution of anhydrous $MeOCH_2CH_2OMe$ (glyme) followed by the reaction of the *N*-lithium derivative that formed with compound **1**

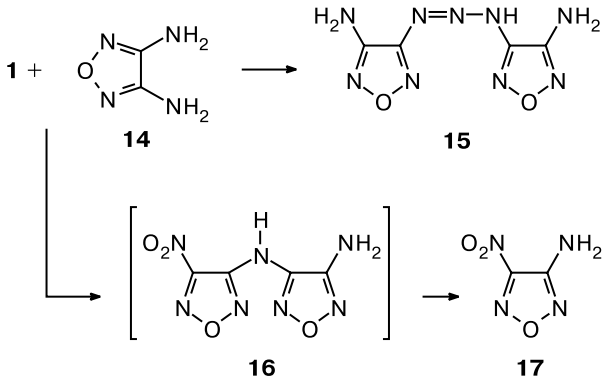
Table 3. IR spectra, ^1H and ^{13}C NMR spectra, and mass spectra of secondary 3-(R-amino)-4-nitrofurazans **2—13**

Compound	IR, ν/cm^{-1}	NMR ($CDCl_3$), δ		MS, *m/z*
		δ_H, *J*/Hz	δ_C	
2	1615, 1530, 1480, 1375, 1355, 1315, 1242, 1210, 1035, 1004	2.99 (d, 2 H, CH_2, J = 5.3); 5.66 (br.s, 1 H, NH)	30.3 (Me), 151.5 (CNO_2), 151.6	144 $[M]^+$, 114 $[M - NO]^+$, 98 $[M - NO_2]^+$
3	3384, 2904, 2872, 1616, 1520, 1456, 1440, 1400, 1360, 1304, 1200, 1064, 1048	4.58 (d, 2 H, CH_2, J = 5.4); 5.83 (s, 1 H, NH); 7.41 (m, 5 H, Ph)	48.5, 128.0, 128.3, 128.9 (Ph), 136.3 (C_i), 150.8, 151.5	220 $[M]^+$, 190 $[M - NO]^+$, 144 $[M - NO - NO_2]^+$
4	3344, 2936, 1616, 1528, 1448, 1400, 1384, 1360, 1312, 1240, 1200, 1040, 1008	2.43 (s, 3 H, Me); 4.72 (d, 2 H, CH_2, J = 6.1); 6.14 (br.s, 1 H, NH)	7.9 (Me), 37.6, 150.1, 150.6, 150.8, 151.5	226 $[M]^+$, 196 $[M - NO]^+$, 166 $[M - 2\ NO]^+$
5	3376, 1636, 1592, 1576, 1552, 1528, 1480, 1448, 1416, 1392, 1348, 1216	4.92 (d, 2 H, CH_2, J = 5.9); 6.47 (br.s, 1 H, NH); 7.52 (m, 3 H, Ph); 8.02 (d, 2 H, Ph, J = 7.3)	39.3, 123.2, 127.0, 129.2, 132.2, 150.6, 151.3, 162.2, 165.8	288 $[M]^+$, 242 $[M - NO_2]^+$
6	3152, 2952, 2920, 1620, 1512, 1480, 1464, 1436, 1392, 1340, 1220, 1192, 1040, 992	3.82, 4.11 (both t, 2 H each, CH_2, J = 6.9); 4.25 (d, 2 H, CH_2, J = 5.9); 7.15 (s, 1 H); 7.32 (t, 1 H, NH, J = 5.9)*	34.9, 41.8, 115.5, 45.9, 141.7, 148.1, 151.0, 152.8*	268 $[M]^+$, 192 $[M - NO - NO_2]^+$
7	3160, 3112, 1620, 1512, 1464, 1440, 1392, 1360, 1344, 1224, 1200, 1160, 1104, 1036	2.38 (s, 3 H, Me); 4.37 (d, 2 H, CH_2, J = 5.9); 7.45 (t, 1 H, NH, J = 5.9); 7.60 (s, 2 H)*	13.6, 42.2, 111.1, 116.6, 125.0, 142.5, 147.3, 151.2, 153.0*	280 $[M]^+$, 204 $[M - NO - NO_2]^+$
8	3425, 3136, 3088, 1624, 1516, 1456, 1432, 1400, 1360, 1336, 1248, 1200, 1044, 984	4.58 (d, 2 H, CH_2, J = 5.7); 7.05 (dd, 1 H, J = 4.5, J = 6.7); 7.68 (t, 1 H, NH, J = 5.7); 7.85 (s, 1 H); 8.49 (m, 1 H); 8.90 (d, 1 H, J = 6.7)*	42.4, 108.7 (C(7)), 108.9 (C(5)), 135.0 (C(6)), 144.3 (C(4)), 147.5 (C(8)), 150.1 (C(9)), 151.3, 153.1*	261 $[M]^+$, 185 $[M - NO - NO_2]^+$
9	3370, 2872, 1605, 1525, 1422, 1338, 1300, 1196, 1061, 980	1.82—2.12 (m, 8 H, CH_2); 3.25 (m, 4 H, CH_2); 4.22 (s, 2 H, CH_2); 6.63 (br.s, 1 H, NH)	23.3, 24.9, 34.8, 36.7, 73.2, 150.8, 151.6	253 $[M]^+$, 207 $[M - NO_2]^+$, 177 $[M - NO - NO_2]^+$
10	3440, 2960, 1688, 1624, 1576, 1520, 1456, 1408, 1384, 1296, 1040, 928, 832	—	—	398 $[M]^+$, 352 $[M - NO_2]^+$, 269, 253, 239, 185, 173, 143, 117, 43
11	3408, 2904, 2848, 1608, 1516, 1448, 1392, 1344, 1328, 1264, 1120, 1092, 1044, 832	1.71, 2.06, 2.18 (s, 15 H, Ad); 5.53 (s, 1 H, NH)	29.5, 36.0, 40.7, 53.3, 148.3, 152.2	264 $[M]^+$, 218 $[M - NO_2]^+$
12a	3416, 2936, 1624, 1520, 1456, 1400, 1376, 1360, 1344, 1320, 1240, 1196, 1128, 1040	3.48 (s, 4 H, CH_2); 7.21 (br.s, 2 H, NH)*	41.8 (CH_2), 151.6, 153.1*	286 $[M]^+$, 240 $[M - NO_2]^+$, 226 $[M - 2\ NO]^+$
12b	3448, 3424, 2944, 1628, 1520, 1480, 1464, 1432, 1392, 1368, 1340, 1280, 1196, 1052	1.53 (m, 2 H, 5); 1.82 (m, 4 H, 4); 3.46 (m, 4 H, 3); 5.49 (br.s, 2 H, NH)	24.0 (C(5)), 28.5 (C(4)), 44.5 (C(3)), 151.1, 151.5	328 $[M]^+$, 282 $[M - NO_2]^+$, 268 $[M - 2\ NO]^+$
13a	3392, 2920, 1620, 1600, 1576, 1548, 1528, 1448, 1376, 1348, 1304, 1204, 1192, 1060, 1044, 968	2.33 (s, 3 H, Me); 6.81—7.34 (m, 4 H, Ph); 7.32 (s, 1 H, NH)	20.9 (Me), 115.2, 118.7, 124.5, 128.4, 137.4, 139.1, 147.2, 151.7	220 $[M]^+$, 174 $[M - NO_2]^+$
13b	3384, 1696, 1560, 1528, 1448, 1384, 1340, 1288, 1228, 1176, 1048, 976	2.29 (s, 3 H, Me); 7.12, 7.43 (both d, 2 H each, Ph, J = 7.2)	18.9 (Me), 117.5, 128.1, 131.5, 134.6, 146.5, 151.4	256 $[M]^+$, 210 $[M - NO_2]^+$
13c	3175, 3610, 1613, 1578, 1561, 1529, 1508, 1495, 1475, 1440, 1371, 1360, 1321, 1270	—	—	—

* The spectrum was recorded for a solution in DMSO-d_6.

at −10 °C and acidification of the reaction mixture afforded 3-amino-4-nitrofurazan (**17**) in 35—40% yield. Presumably, the reaction proceeds through the intermediate formation of secondary amine **16**, which decomposes to give more stable primary amine **17**.

Scheme 3

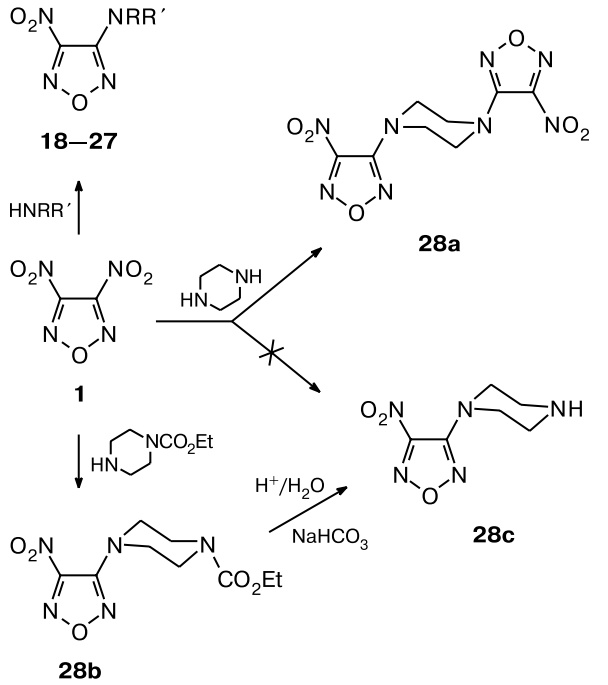


The reactions of compound **1** with secondary alkylamines produce the corresponding trisubstituted furazan-containing amines **18—27** (Scheme 4). However, the nitro group that is replaced in these reactions also initiates side reactions, and the starting alkylamines are partially consumed for the formation of the corresponding nitrosoamines. In spite of the fact that nitrosoamines can easily be separated from the product of the major reaction with the use of standard methods, the formation of these toxic compounds is highly undesirable. The target compounds can be prepared in yields of higher than 70% under slightly modified reaction conditions analogous to those mentioned above (Table 4). However, the method *D*, which provides suppression of the side formation of nitrosoamines, is a procedure of choice for these reactions.

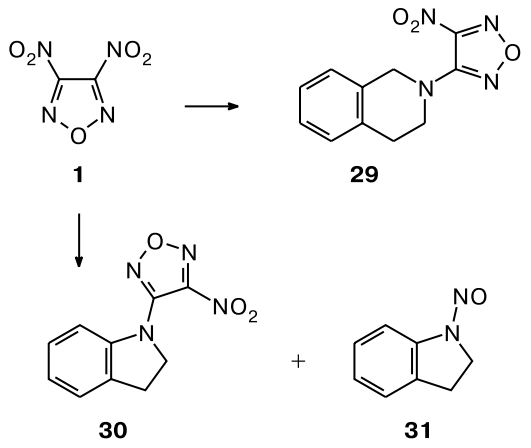
Attempts to synthesize monosubstituted piperazine **28c** by the reaction of dinitro compound **1** with 1—3 moles of piperazine in the presence of a base (method *C*) led to the preparation of a complex mixture of products, from which only disubstitution product **28a** was isolated (in a yield of no higher than 30%). Under analogous conditions, the yield of compound **28a** in the reaction with 0.5 mole of piperazine increased to 85%. Compound **28c** was synthesized in two steps using monoprotected piperazine (see Scheme 4). The protective group in derivative **28b** is efficiently removed with 20% perchloric acid on heating.

It should be noted that the ability of the starting secondary amines to undergo *N*-nitrosation is determined by their structures. For example, tetrahydroisoquinoline smoothly reacts with dinitrofurazan **1** to give compound **29** (60—86%) and *N*-nitrosotetrahydroisoquinoline (~5%). To the contrary, the reaction with indolizine (Scheme 5) affords product of nucleophilic substitution **30** in low yield (up to 27%) along with a large amount of nitrosoamine **31** (in a yield of up to 50%), which complicates isolation of the target product. The method *D* proved to be also inefficient in the synthesis of compound **30**. In this case, product **30** was prepared in low yield (16%) and the side reaction giving rise to nitrosoamine **31** (7%) was incompletely suppressed.

Scheme 4

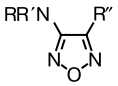


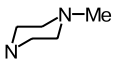
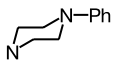
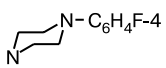
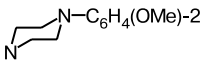
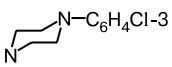
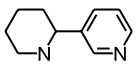
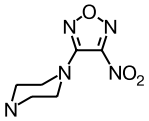
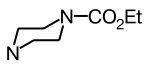
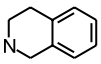
Scheme 5



Like compound **1**, other 3-nitro-4-R-furazans containing electron-withdrawing substituents R (Scheme 6) readily react with amines. For instance, both nitro groups in compounds **32** and **35** were replaced upon treatment

Table 4. Physicochemical characteristics of tertiary aminofurazans **18—30**

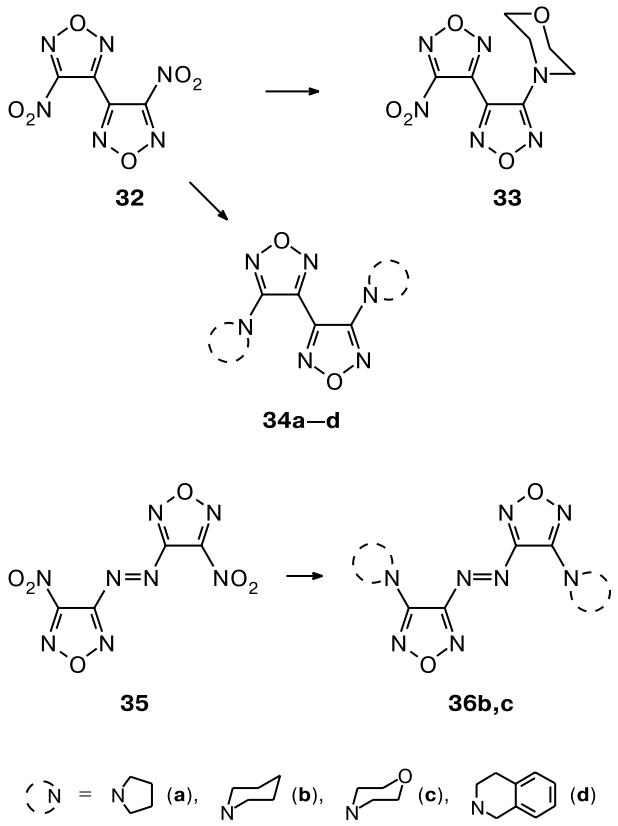


Compound	NRR′	R″	Yield (%) (Method)	M.p./°C	Found / Calculated (%) C	H	N	Molecular formula (mol. weight)	MS, *m/z*
18		NO_2	83 (*A*) 71 (*B*) 68 (*C*) 72 (*D*)	Oil	42.49 42.41	5.12 5.09	28.20 28.28	$C_7H_{10}N_4O_3$ (198.08)	198 $[M]^+$, 152 $[M - NO_2]^+$
19		NO_2	0 (*B*) 72 (*C*) 52 (*D*)	49—51.5 (MeOH)	39.80 39.61	3.87 3.80	26.37 26.41	$C_7H_8N_4O_4$ (212.06)	212 $[M^+]$, 136 $[M - NO - NO_2]^+$
20		NO_2	56 (*B*) 64 (*D*)	Oil	33.41 33.33	3.77 3.73	25.88 25.93	$C_6H_8N_4O_3S_1$ (216.03)	216 $[M^+]$, 170 $[M - NO_2]^+$
21		NO_2	75 (*A*) 68 (*B*) 72 (*D*)	57—58 (hexane)	36.11 35.99	4.10 4.03	27.02 28.00	$C_6H_8N_4O_4$ (200.06)	200 $[M^+]$, 154 $[M - NO_2]^+$
22		NO_2	42 (*A*) 81 (*B*) 57 (*C*)	49—50 (CH_2Cl_2)	39.57 39.44	5.31 5.20	32.94 32.85	$C_7H_{11}N_5O_3$ (213.20)	213 $[M]^+$
23		NO_2	85 (*B*) 87 (*C*) 91 (*D*)	136—137 (CCl_4)	52.49 52.36	4.94 4.76	25.28 25.44	$C_{12}H_{13}N_5O_3$ (275.27)	275 $[M]^+$
24		NO_2	84 (*B*) 81 (*D*)	109—110 (CCl_4)	49.23 49.15	4.28 4.12	23.76 23.88	$C_{12}H_{12}N_5O_3F$ (293.26)	293 $[M]^+$
25		NO_2	52 (*B*) 79 (*D*)	101—102 (CCl_4)	51.32 51.15	5.04 4.95	22.81 22.94	$C_{13}H_{15}N_5O_4$ (305.29)	305 $[M]^+$
26		NO_2	82 (*B*) 93 (*D*)	124—125 (CCl_4)	46.70 46.54	4.04 3.91	22.45 22.61	$C_{12}H_{12}N_5O_3Cl$ (309.71)	309 $[M]^+$
27		NO_2	5 (*B*) 93 (*C*) 84 (*D*)	Oil	52.42 52.34	4.83 4.76	24.28 25.45	$C_{12}H_{13}N_5O_3$ (275.1)	275 $[M^+]$, 199 $[M - NO - NO_2]^+$
28a		NO_2	54 (*B*) 85 (*C*) 41 (*D*)	141—144 ($CHCl_3$)	30.84 30.76	2.65 2.58	35.86 35.90	$C_8H_8N_8O_6$ (312.06)	312 $[M^+]$, 266 $[M - NO_2]^+$, 252 $[M - 2\ NO]^+$
28b		NO_2	68 (*B*) 53 (*C*) 72 (*D*)	73—74 (hexane)	39.88 39.85	4.86 4.83	25.78 25.82	$C_9H_{13}N_5O_5$ (271.23)	271 $[M^+]$, 225 $[M - NO_2]^+$
28c		NO_2	77*	34—36 (Pr^iOH)	36.16 36.18	4.58 4.55	35.11 35.16	$C_6H_9N_5O_3$ (199.17)	199 $[M^+]$, 153 $[M - NO_2]^+$
29		NO_2	64 (*A*) 60 (*B*) 71 (*C*) 86 (*D*)	153—154 (hexane)	53.75 53.64	4.12 4.10	22.65 22.76	$C_{11}H_{10}N_4O_3$ (246.08)	246 $[M^+]$, 170 $[M - NO - NO_2]^+$
30		NO_2	27 (*A*) 24 (*B*) 16 (*D*)	109—118 (hexane)	51.84 51.71	3.50 3.47	24.01 24.14	$C_{10}H_8N_4O_3$ (232.06)	232 $[M^+]$, 156 $[M - NO - NO_2]^+$

* See Scheme 4.

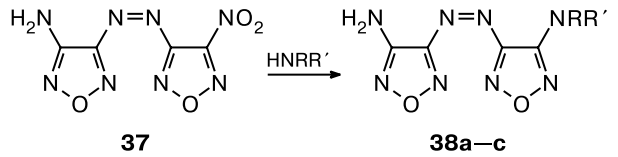
with an excess of secondary amines in $CHCl_3$ at room temperature over several minutes to give diamines **34a—d** and **36b,c**, respectively, in 74—95% yields (see Scheme 6). The reactions of equimolar amounts of bifurazan **32** and morpholine in the presence of Et_3N afforded a complex mixture from which monosubstitution product **33** was isolated in 7% yield. Attempts to prepare monosubstitution products from azo compound **35** were unsuccessful.

Scheme 6



Unsymmetrical amines **38a—c** were prepared in 78—81% yields by treatment of mononitro compound **37** with an excess of the corresponding amine in acetonitrile or DMSO (Scheme 7).

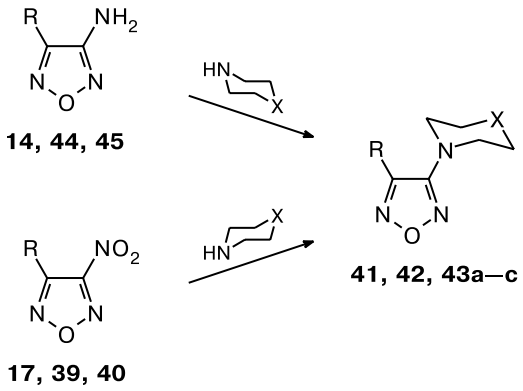
Scheme 7



NRR′ = $N(CH_2)_5$ (**a**), $N(CH_2CH_2)_2O$ (**b**), NBu_2 (**c**)

The nitro group at the furazan ring containing an electron-donating substituent (compounds **17**, **39**, and **40**) is replaced with secondary amine only upon prolonged heating in an excess of the latter (Scheme 8). The yields of products **41—43** were no higher than 40%. 3-Methyl-4-nitrofurazan (**40**) reacts in a similar fashion with all amines under study, whereas 4-nitro-3-phenylfurazan (**39**) smoothly reacts only with *N*-methylpiperazine. Heating of compound **39** in morpholine gave rise to a complex mixture. We failed to isolate the target product from this mixture.

Scheme 8

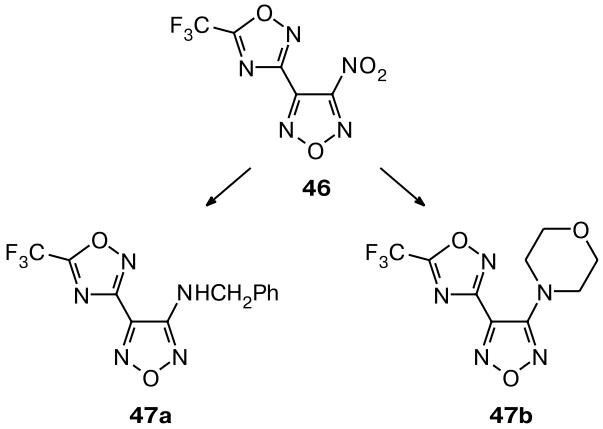


R = NH_2 (**14**, **17**, **41**), Ph (**39**, **42**, **44**), Me (**40**, **43a—c**, **45**);
X = CH_2 (**41**), NMe (**42**, **43a**), NH (**43b**), O (**43c**)

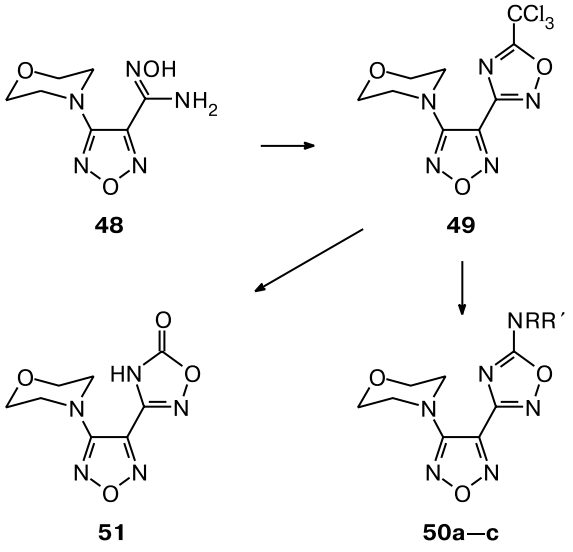
It should be noted that compounds **41—43** were also prepared, although in low yields (3—10%), by heating aminofurazans **14**, **44**, and **45**, respectively, in solutions of the corresponding secondary amines in an autoclave at 150—160 °C (the reaction conditions of transamination were not optimized).

The reactions of nitro compound **46** both with primary and secondary alkylamines are accompanied by the opening of the 1,2,4-oxadiazole ring as a side process giving rise to a complex mixture of products. Chromatographic separation afforded the target products **47a** and **47b** in 22 and 30% yields, respectively (Scheme 9). How-

Scheme 9



Scheme 10

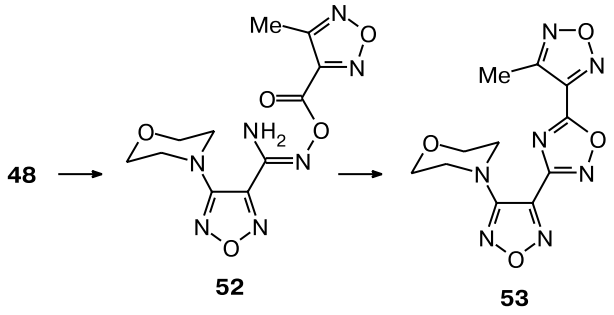


R = H, R′ = Bn (**a**), $CH_2CH_2NMe_2$ (**b**); R—R′ = $(CH_2)_5$ (**c**)

ever, this method is unsuitable for the synthesis of analogs of compounds **47** in which the CF_3 group is replaced by the Me or CCl_3 groups because the corresponding starting compounds are subjected to deeper transformations under the action of nucleophiles.

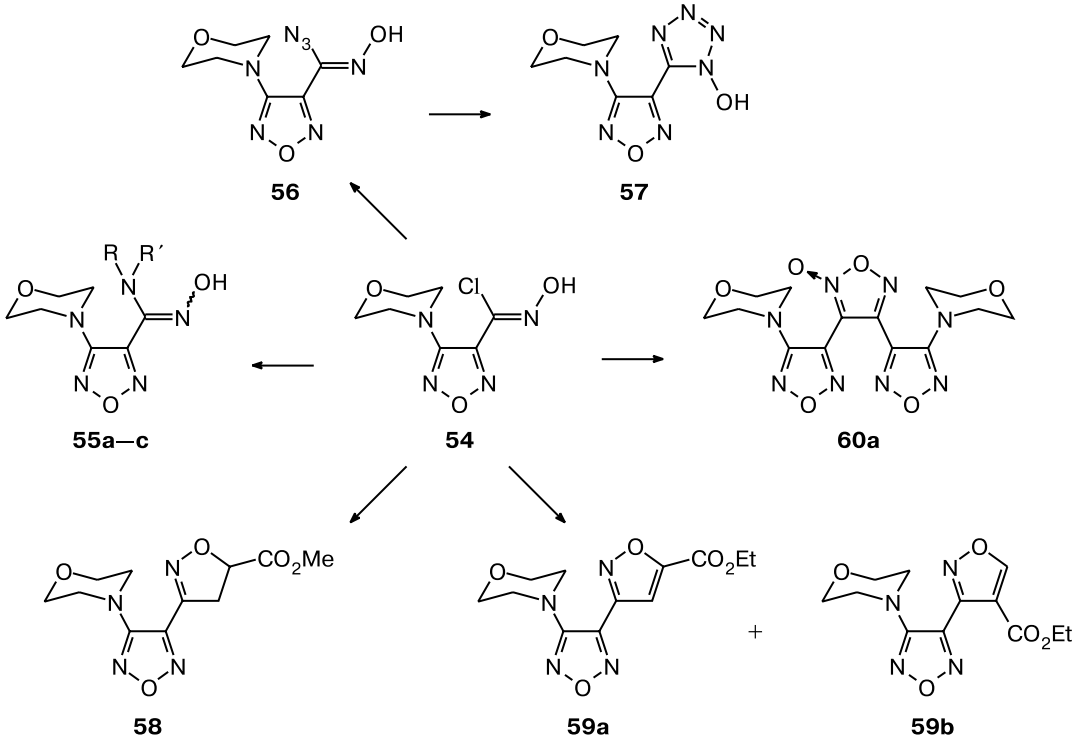
An alternative approach to the synthesis of analogs of compound **47b** and various 4-(hetaryl)-3-(RR″N)-

Scheme 11



furazans is based on the use of readily accessible furazanylamidoximes.[3,9,10] For example, heating of amidoxime **48** with trichloroacetyl chloride for 40 min was accompanied by cyclization to form 1,2,4-oxadiazole **49** in 82% yield (Scheme 10). The trichloromethyl group in this compound is readily replaced by treating with primary or secondary amines. Refluxing of the reagents in anhydrous THF over a short period produces substitution products **50a—c** in ~60% yields. In the presence of moisture, the reaction is accompanied by hydrolytic elimination of the CCl_3 group as a side process. As a result, the reaction affords amines **50a—c** along with a substantial amount of oxadiazolone **51** (see Scheme 10). Oxadiazolone **51** was prepared as the major product (in 86% yield) by the reaction of compound **49** with a 10% aqueous solution of alkali.

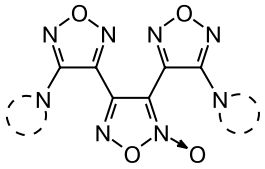
Scheme 12



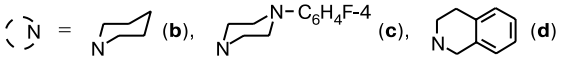
Acylation of amidoxime **48** with 3-methylfurazanocarboxylic acid in the presence of carbodiimide yielded compound **52**, which underwent cyclization to 1,2,4-oxadiazole **53** (Scheme 11) upon refluxing in DMF for 5 min.

Diazotization of compound **48** (and its analogs, see the Experimental section) according to a procedure developed earlier[11] led to the replacement of the amino group of the amidoxime fragment with chlorine to give the corresponding hydroxamic acid chloride **54** in 75—90% yield. Possible transformations of compound **54** into various tertiary aminofurazans are presented in Scheme 12.

It is known that the reactions of hydroxamic acid chlorides with amines proceed through the intermediate formation of nitrile oxide, which reacts with the second amine molecule to give the corresponding amidoxime. Compounds **55a—c** were prepared in ~80% yields. The azide ion readily replaces the chlorine atom in compound **54** to give azide oxime **56**. The latter undergoes cyclization to tetrazole **57** in 86% yield upon treatment with dry HCl. In the presence of dipolarophiles, nitrile oxide, which is generated from compound **54** under the action of bases, is involved in 1,3-dipolar cycloaddition to form isoxazoles **58** and **59a,b**. In the absence of a dipolarophile, nitrile oxide is dimerized to give furoxan **60a** in 76% yield. Furoxans **60b—d** containing other amino fragments were prepared analogously.



60b—d

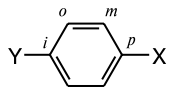


The structures of the secondary and tertiary aminofurazans synthesized were confirmed by elemental analysis, NMR and IR spectroscopy, and mass spectrometry (EI). The structures of compounds **3**, **29**, **38b**, **53**, **57**, and **59a** were established by X-ray diffraction analysis.

The mass spectra of all amines have intense molecular ion peaks. The main path of fragmentation under electron impact is associated with the cleavage of the furazan ring through elimination of the NO molecule to give the $[M - NO]^+$ ions. Aminonitrofurazans undergo specific fragmentation under electron impact. The molecular ions of these compounds readily lose the NO_2 molecule. In these cases, synchronous elimination of both NO and NO_2 is often observed resulting in the formation of the $[M - NO - NO_2]^+$ ions.

The ^{14}N NMR spectra of nitrofurazans **2—30** are characterized by the presence of a narrow ($\Delta\eta_{1/2}$ = 9—25 Hz) singlet of the nitrogen atom of the nitro group in the region from −32 to −33.5 ppm. In the ^{13}C NMR spectra, the signal of the carbon atom bound to the nitro group is strongly broadened due to $^{13}C—^{14}N$ coupling. The influence of the nitro group is also manifested even at a distance of two bonds resulting in a slight broadening of the signal of the β-carbon atom (with respect to NO_2). For ease of assigning the signals in the ^{13}C NMR spectra, we synthesized a series of compounds containing the invariable tertiary nitrogen atom involved in the morpholine fragment. The spectroscopic data for these compounds are given in Table 5. The assignment of the signals of the carbon atoms of the furazan ring was made taking into account the additive influence of the substituents based on the spectroscopic features revealed earlier.[12—14] These data provide the basis for the assignment of the signals of the carbon atoms in other compounds synthesized in the present study (see the Experimental section).

Recently,[14,15] we have demonstrated that Lynch' equation[16] (1) can be used for predicting the ^{13}C NMR chemical shifts of the atoms of the furazan ring in a series of disubstituted furazans containing one invariable substituent based on abundant published data on the increments of substituents in monosubstituted benzenes. This simple linear equation (1) relates the ^1H and ^{13}C chemical shifts of the atoms in *para*-disubstituted benzenes, which contain the fixed substituent Y and various substituents X, to the increments of these substituents in monosubstituted benzenes.



$$Shift_X(Y) = a + b \cdot SCS_X(H), \quad (1)$$

where $Shift_X(Y)$ is the chemical shift of the C_X atom in a series of disubstituted benzenes containing the fixed substituent Y, $SCS_X(H)$ is the corresponding increment of the substituent X in monosubstituted benzene (at Y = H), *a* and *b* are coefficients of the equation of linear regression.

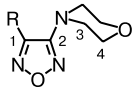
Following this methodology, we determined the coefficients of Eq. (2) for (morpholin-1-yl)furazans with the use of the data given in Table 5. The revealed dependence allowed us to calculate the chemical shifts for the C(1) atom* of the furazan ring in this series of compounds with a high degree of accuracy.

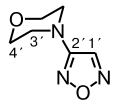
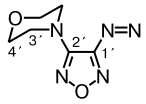
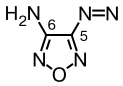
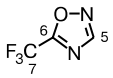
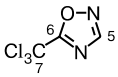
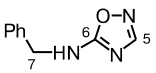
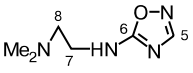
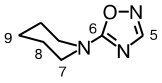
$$\delta(C(1))(R) = a + b \cdot SCS_{ipso}(R), \quad (2)$$

$a = 139.0 \pm 0.6$, $b = 0.66 \pm 0.04$ (the correlation coefficient $r = 0.984$, $n = 6$).

Earlier,[14,15] we have noted that the linear regression, which describes the changes in the chemical shift of the C(2) atom in furazans, is characterized by a relatively low correlation coefficient. This is associated with a rather

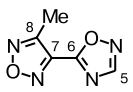
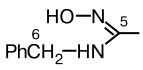
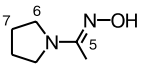
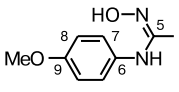
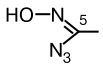
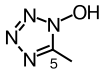
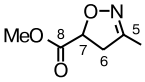
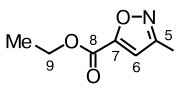
* The atomic numbering scheme is given in Table 5.

Table 5. Spectroscopic characteristics of 3-(morpholin-1-yl)-4-R-furazans 

Compound	R	^{13}C NMR ($CDCl_3$), δ			^{1}H NMR ($CDCl_3$), δ, *J*/Hz	IR, ν/cm^{-1}
		C(1) (C(2))	C(3) (C(4))	R		
21	NO_2	153.4 (152.5)	48.7 (65.4)	—	3.33, 3.85 (t, 4 H, CH_2, *J* = 4.5) 1120, 1064, 1028, 920, 824	2984, 2864, 1680, 1588, 1480, 1448, 1368, 1352, 1264, 1204,
33		133.9 (159.0)	49.2 (65.6)	139.3 (C(5)), 160.1 (C(6))	3.19 (br.s, 4 H, C(4)H_2); 3.77 (br.s, 4 H, C(3)H_2)	2940, 2860, 2830, 1625, 1555, 1525, 1430, 1350, 1275, 1255, 1140, 1125, 1100, 1000, 980, 910
34c		137.1 (158.9)	48.4 (65.2)	—	—	3424, 3016, 2936, 1688, 1548, 1456, 1376, 1344, 1304, 1272, 1256, 1232, 1216, 1152, 1120, 1088, 1048, 984
36c		156.6 (156.7)	48.2 (66.2)	—	3.64, 3.87 (both br.s, 4 H each, CH_2)	2990, 2350, 1508, 1464, 1420, 1388, 1344, 1284, 1148, 1084, 976, 876
38b		155.5 (157.7)	48.3 (65.8)	154.0 (C(5)), 148.6 (C(6))	—	—
43c	Me	144.5 (159.5)	48.8 (66.0)	10.0	2.35 (s, 3 H, Me); 3.25 (t, 4 H, C(4)H_2, *J* = 4.8); 3.81 (t, 4 H, C(3)H_2, *J* = 4.8)	3448, 3008, 2968, 2912, 2864, 1584, 1508, 1456, 1408, 1392, 1376, 1296, 1268, 1240, 1216, 1116, 1056, 1040, 984, 920
47b		140.5 (158.7)	49.9 (66.3)	115.5 (C(7)), 166.8 (C(6)), 159.4 (C(5))	3.46 (t, 4 H, C(4)H_2, *J* = 4.8); 3.90 (t, 4 H, C(3)H_2, *J* = 4.8)	2965, 2889, 2810, 1601, 1545, 1525, 1428, 1360, 1295, 1250, 1200, 1150, 1000, 983, 840
49		—	—	—	3.33, 3.65 (both br.s, 4 H each, CH_2)	1596, 1560, 1532, 1278, 1261, 1151, 1119, 1076, 1060, 1015, 970, 918, 900, 881, 896, 819, 796, 762, 730, 700, 680
50a		138.8 (158.8)	48.7 (65.2)	46.7 (C(7)), 128.5, 127.2, 127.4, 137.9 (Ph), 158.8 (C(5)), 171.9 (C(6))	3.27, 3.65 (both br.s, 4 H each, CH_2); 4.54 (d, 2 H, CH_2, *J* = 4.0); 7.27 (c, 5 H, C_6H_5); 9.38 (br.s, 1 H, NH).	—
50b		138.8 (158.8)	48.7 (65.2)	41.2 (Me), 45.0 (C(8)), 57.6 (C(7)), 158.8 (C(5)), 171.7 (C(6))	2.11 (s, 6 H, CH_3); 2.38 (t, 2 H, CH_2, *J* = 6.3); 3.27 (m, 6 H, CH_2); 3.67 (s, 4 H, CH_2); 8.73 (br.s, 1 H, NH)	3210, 1675, 1589, 1521, 1344, 1280, 1267, 1176, 1158, 1121, 1071, 1040, 1019, 970, 910, 890, 878, 847, 775, 822
50c		138.9 (159.1)	46.8 (65.3)	22.9 (C(9)), 24.6 (C(8)), 48.8 (C(7)), 158.1 (C(5)), 170.7 (C(6))	1.60 (m, 6 H, CH_2); 3.27 (s, 4 H, CH_2); 3.60, 3.69 (both m, 4 H each, CH_2)	1645, 1581, 1530, 1333, 1283, 1271, 1260, 1172, 1115, 1071, 1061, 1050, 1029, 1016, 990, 970, 905, 890, 851, 844, 770

(*to be continued*)

Table 5 (*continued*)

Compound	R	^{13}C NMR ($CDCl_3$), δ			^{1}H NMR ($CDCl_3$), δ, *J*/Hz	IR, ν/cm^{-1}
		C(1) (C(2))	C(3) (C(4))	R		
51		136.7 (158.9)	48.9 (65.2)	149.0 (C(6)), 158.2 (C(5))	3.29, 3.67 (both s, 4 H each, CH_2)	1800, 1618, 1550, 1305, 1270, 1260, 1237, 1151, 1105, 1060, 1012, 942, 914, 890, 850, 841, 792, 755, 668
53		137.8 (159.5)	48.3 (65.3)	9.0 (Me), 143.6 (C(7)), 152.1 (C(8)), 158.9 (C(5)), 167.0 (C(6))	2.69 (s, 3 H, CH_3); 3.16, 3.74 (both t, 4 H each, CH_2, *J* = 4.5)	1638, 1591, 1530, 1278, 1269, 1158, 1112, 1099, 1071, 1058, 1020, 976, 922, 909, 851, 779
55a		140.2 (158.5)	47.4 (65.1)	45.8 (C(6)), 126.9, 127.1, 128.3, 140.5 (Ph), 142.9 (C(5))	<u>*Z*</u>-isomer: 3.00, 3.49 (both s, 4 H each, CH_2); 4.07 (d, 2 H, CH_2, *J* = 6.7); 6.91—7.33 (m, 6 H, C_6H_5, NH); 10.32 (s, 1 H, OH) <u>*E*</u>-isomer: 3.16 (s, 4 H, CH_2); 4.22 (d, 2 H, CH_2, *J* = 6.0); 9.40 (s, 1 H, OH)	3358, 3205, 1655, 1573, 1310, 1270, 1120, 1070, 1010, 980, 923, 895, 783, 735, 698
55b		139.2 (158.1)	47.6 (65.3)	24.9 (C(7)), 49.6 (C(6)), 142.7 (C(5))	1.69, 3.24, 3.36, 3.64 (all m, 4 H each, CH_2); 9.91 (s, 1 H, OH)	3150, 1650, 1578, 1530, 1410, 1309, 1285, 1270, 1215, 1142, 1118, 1075, 1100, 965, 930, 871, 850
55c		139.7 (158.2)	47.6 (65.2)	55.2 (Me), 113.9 (C(8)), 123.8 (C(7)), 132.8 (C(6)), 141.5 (C(5)), 155.6 (C(9))	<u>*Z*</u>-isomer: 3.11, 3.56 (both s, 4 H each, CH_2); 3.62 (s, 3 H, CH_3); 6.69 (s, 4 H, C_6H_4); 8.62 (s, 1 H, NH); 10.72 (s, 1 H, OH) <u>*E*</u>-isomer: 6.80, 7.40 (both d, 2 H each, C_6H_2, *J* = 8.1); 9.87 (s, 1 H, OH)	3350, 3280, 1637, 1581, 1531, 1513, 1328, 1290, 1278, 1261, 1240, 1167, 1111, 1071, 1029, 1002, 941, 925, 880, 872, 842, 830, 800, 765
56		—	—	—	3.09, 3.70 (both s, 4 H each, CH_2); 12.32 (s, 1 H, OH)	3200 (OH), 2161 (N_3), 2131, 2097, 1613 (C=NOH), 1542, 1510, 1310, 1283, 1262, 1248, 1161,1110, 1078, 1066, 1019, 965, 933, 915, 902, 885, 862, 855, 844
57		137.5 (158.9)	48.5 (65.3)	135.0 (C(5))	3.20, 3.67 (both t, 4 H each, CH_2, *J* = 4.2); 11.60 (s, 1 H, OH)	2700 (OH), 1559, 1302, 1365, 1169, 1110, 1065, 1035, 1020, 999, 910, 880
58		140.9 (158.4)	49.1 (65.2)	39.5 (C(6)), 52.4 (Me), 77.8 (C(7)), 147.5 (C(5)), 169.5 (C(8))	3.27, 3.65 (both t, 4 H each, CH_2, *J* = 4.4); 3.67 (s, 3 H, CH_3); 3.76 (m, 2 H, CH_2); 5.53 (m, 1 H, CH)	1750, 1542, 1505, 1310, 1282, 1265, 1220, 1160, 1118, 1027, 1008, 919, 895, 861, 841, 700
59a		139.3 (158.6)	48.8 (65.1)	13.8 (Me), 62.4 (C(9)), 109.7 (C(6)), 152.7 (C(8)), 155.5 (C(5)), 161.1 (C(7))	1.16 (t, 3 H, CH_3, *J* = 7.4); 3.06, 3.57 (both t, 4 H each, CH_2, *J* = 4.4); 4.23 (q, 2 H, CH_2, *J* = 4.4); 9.98 (s, 1 H, CH)	3100, 1720, 1779, 1755, 1406, 1321, 1305, 1282, 1177, 1117, 1085, 1070, 1032, 1018, 1000, 965, 918, 868, 846, 780

narrow range of changes in the chemical shift of the C(2) atom. In the spectra of (morpholin-1-yl)furazans under consideration, the chemical shift of the signal of the C(2) atom changes by no more than 2 ppm (δ 157—159) (see Table 5). The only exception is 3-(morpholin-1-yl)-4-nitrofurazan (**21**) in which the strong electron-withdrawing effect of the nitro group leads to a noticeable upfield shift of the signal of the C(2) atom (δ 152.5). The constancy of the chemical shift for the C(2) atom of the furazan ring bound to a particular substituent is indicative of a relatively weak influence of the second substituent at the C(1) atom on the electron density redistribution. This facilitates the assignment of the signals in the spectra.

X-ray diffraction analysis of compounds **3**, **29**, **38b**, **53**, **57**, and **59a** unambiguously confirmed the assumed structures of the reaction products (Fig. 1—6). The bond lengths in the furazan ring at the amino center are given in Table 6. The main crystallographic characteristics of these compounds are listed in Table 7.

In all the compounds under consideration, the amino nitrogen atom of the substituent (except for the amino group) has a pyramidal configuration; the sum of the bond angles at the nitrogen atom is in the range of 339—352°.

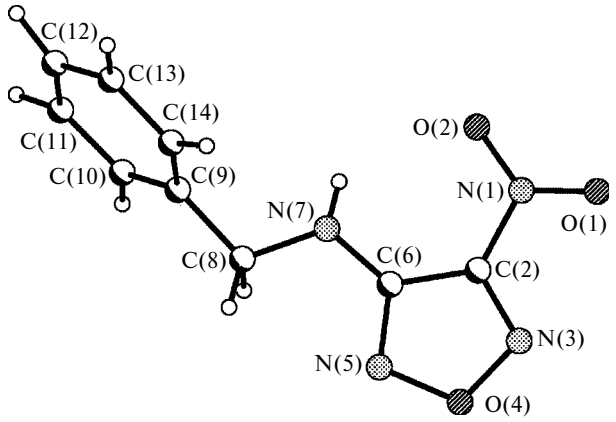


Fig. 1. Molecular structure of compound **3**.

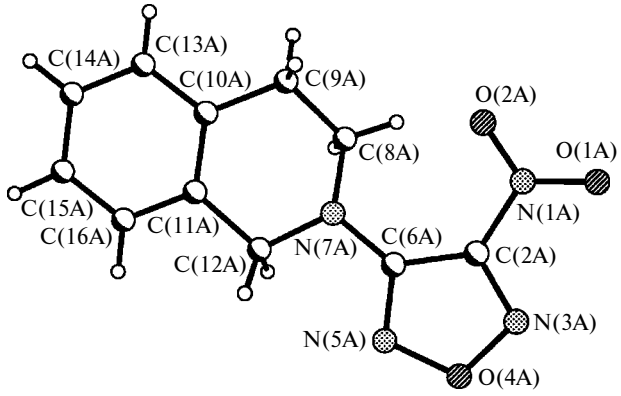


Fig. 2. Molecular structure of compound **29**.

The maximum value is observed for the structure of **3**. This is, apparently, associated with the conjugation between the secondary nitrogen atom and the π system of the furazan ring, which is more pronounced than that between the furazan ring and the tertiary nitrogen atom in other five structures. This fact is confirmed by the

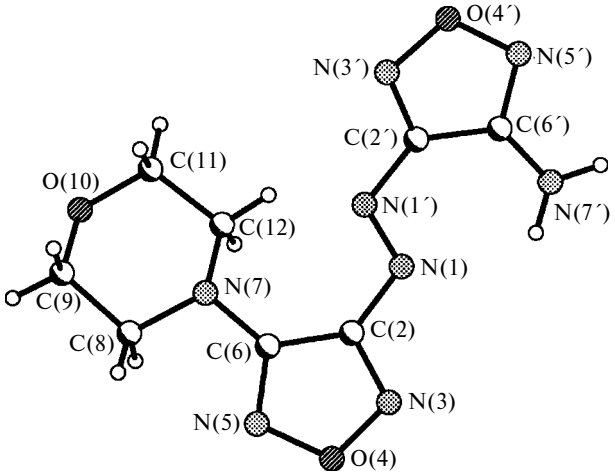


Fig. 3. Molecular structure of compound **38b**.

Bond lengths (*d*) in the second furazan ring:

Bond	*d*/Å	Bond	*d*/Å
C(2′)—C(6′)	1.440(2)	C(6′)—N(7′)	1.336(2)
C(2′)—N(3′)	1.305(2)	N(3′)—O(4′)	1.354(2)
C(6′)—N(5′)	1.312(2)	N(5′)—O(4′)	1.410(2)

The difference between the N—O bond lengths is 0.056 Å.

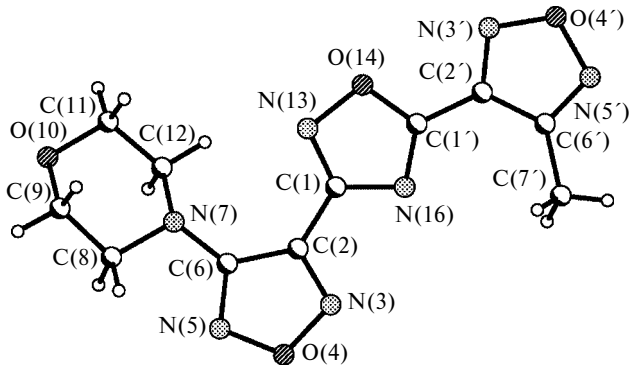


Fig. 4. Molecular structure of compound **53**.

Bond lengths (*d*) in the second furazan ring:

Bond	*d*/(Å)	Bond	*d*/(Å)
C(2′)—C(6′)	1.423(2)	N(3′)—O(4′)	1.365(2)
C(2′)—N(3′)	1.303(3)	N(5′)—O(4′)	1.399(2)
C(6′)—N(5′)	1.298(2)		

The difference between the N—O bond lengths is 0.034 Å.

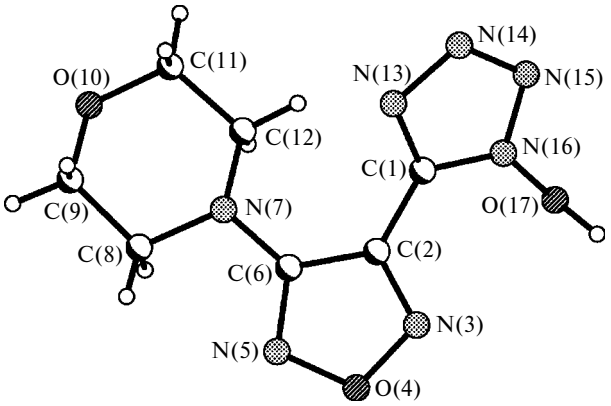


Fig. 5. Molecular structure of compound **57**.

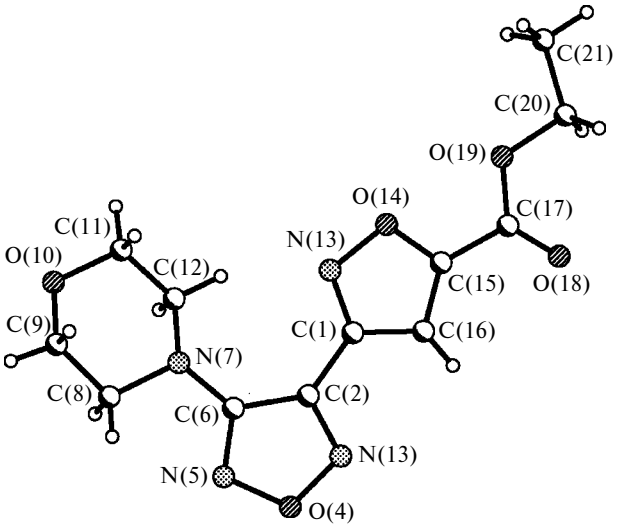


Fig. 6. Molecular structure of compound **59a**.

C(6)—N(7) bond lengths. In molecules **29**, **38b**, **53**, **57**, and **59a**, this bond is in the range of 1.363—1.379 Å, whereas this bond in molecule **3** is shortened (1.336 Å). A similar bond length is observed between the furazan ring and the amino group (C(6′)—N(7′)) in molecule **38b** (see Fig. 3).

Conjugation between the furazan ring and the nitrogen atom of the substituent at the C(6) atom affects primarily the bond lengths at this atom, *viz.*, C(6)—N(5) and C(6)—C(2) (see Table 6). In compounds **38b**, **53**, **57**, and **59a**, the C(6)—N(5) bond is elongated to 1.310—1.314 Å and the C(6)—C(2) bond in the furazan ring is elongated to 1.436—1.450 Å. For comparison, the C(6′)—N(5′) and C(6′)—C(2′) bond lengths in the furazan ring, which bears the methyl group (see Fig. 4, compound **53**) and in which conjugation with the substituent is lacking, have the smallest values (1.298(3) and 1.423(3) Å, respectively). In compounds **3** and **29**, the C(6)—C(2) bond length (1.428—1.429 Å) is virtually equal to that in the nonconjugated fragment. However, the C(6)—N(5) bond length (1.320(3) Å) in these molecules is larger than that in compounds **38b**, **53**, **57**, and **59a**. Presumably, the C(6)—C(2) bond in molecules **3** and **29** is not elongated because these molecules contain the electron-donating substituent at the C(6) atom along with the electron-withdrawing nitro group at the C(2) atom of the furazan ring. It should be noted that the effect of shortening of the bond adjacent to the electron-withdrawing substituent is known for the benzene ring.[17]

In the study,[18] it has been noted that the longer N—O bond in the furazan ring is located closer to a more electron-donating (in relative units) substituent. This fact was confirmed in our recent study.[19] It can be hypothesized that the difference between the N—O bond lengths in the furazan ring will inrease with increasing difference in the electronic effect of the substituents. Actually, this assumption is true for the compounds under study (see Table 6). However, it should be noted that the maximum difference (0.056 Å) is observed in compound **38b** for the furazan ring, in which both substituents possess strong electron-withdrawing properties (see Fig. 3).

The geometry of the molecules and the crystal packings of these compounds are typical of this type of organic compounds. In the crystal structure of compound **29**,

Table 6. Bond lengths (d/Å) in the furazan ring at the amino center in the structures of **3**, **29**, **38b**, **53**, **57**, and **59a**

Bond	**3**	**29***	**38b**	**53**	**57**	**59a**
C(2)—C(6)	1.428(3)	1.429(2)	1.446(2)	1.447(2)	1.436(3)	1.450(2)
C(2)—N(3)	1.301(3)	1.301(2)	1.311(2)	1.303(2)	1.304(3)	1.305(2)
C(6)—N(5)	1.320(3)	1.320(2)	1.310(2)	1.312(2)	1.311(3)	1.314(2)
C(6)—N(7)	1.336(3)	1.363(2)	1.376(2)	1.379(2)	1.372(3)	1.367(2)
N(3)—O(4)	1.360(3)	1.357(2)	1.351(2)	1,368(2)	1.369(2)	1.369(2)
N(5)—O(4)	1.408(3)	1.402(2)	1.398(2)	1.387(2)	1.397(2)	1.395(2)
(ΔN—O)**	(0.048)	(0.045)	(0.047)	(0.019)	(0.028)	(0.026)

* There are four crystallographically independent molecules in the unit cell of the structure of **29**; the bond lengths in these molecules are equal to within the experimental error. The table gives the average bond lengths.

** The difference between the N—O bond lengths.

Table 7. Crystallographic characteristics and details of X-ray diffraction study and structure refinement for compounds **3**, **29**, **38b**, **53**, **57**, and **59a**

Parameter	**3**	**29**	**38b**	**53**	**57**	**59a**
Molecular formula	$C_9H_8N_4O_3$	$C_{11}H_{10}N_4O_3$	$C_8H_{10}N_8O_3$	$C_{11}H_{11}N_7O_4$	$C_7H_9N_7O_3$	$C_{12}H_{14}N_4O_5$
Molecular weight	220.19	246.23	266.24	305.27	239.21	294.27
Crystal system			Monoclinic			
Space group	*Cc*	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$C2/c$
a/Å	10.532(2)	13.895(1)	15.593(3)	22.69(2)	7.320(1)	11.073(3)
b/Å	8.279(2)	12.241(1)	4.202(1)	7.261(5)	20.320(2)	9.822(2)
c/Å	11.742(2)	25.923(2)	18.150(4)	7.931(6)	6.785(1)	24.417(5)
β/deg	107.087(4)	100.855(2)	109.04(3)	91.33(1)	94.757(3)	97.328(6)
V/Å^3	978.7(3)	4330.2(6)	1124.2(4)	1306(2)	1005.7(2)	2633.8(10)
Z	4	16	4	4	4	8
μ(Mo-Kα)/cm^{-1}	1.16	1.14	1.25	1.23	1.28	1.18
d_{calc}/g cm^{-3}	1.494	1.511	1.573	1.552	1.580	1.484
$2\theta_{max}$/deg	60	60	52	60	56	56
Number of reflections	3773	35162	2295	19523	6007	7890
Number of independent reflections	1821	12556	2211	3799	2411	3135
R_{int}	0.0229	0.0359	0.0405	0.0503	0.0280	0.0244
Number of reflections with $I \geq 2\sigma(I)$	1622	7080	1713	2268	1626	2057
Number of parameters	177	881	212	243	190	246
R ($F^2 \geq 2\sigma(F^2)$)	0.0479	0.0500	0.0333	0.0581	0.1505	0.0477
$wR(F^2)$, based on all reflections	0.1312	0.1330	0.0889	0.1457	0.0837	0.1241

there are four independent molecules (see Table 6), but they have similar geometric characteristics and adopt similar conformations.

To summarize, we demonstrated that the nucleophilic displacement of the nitro group at the furazan ring with primary and secondary amines provides an efficient approach to the synthesis of secondary and tertiary aminofurazans. In addition, transformations of the amidoxime fragment bound to the furazan ring and containing the amino substituent allow one to substantially expand the spectrum of polyfunctional derivatives. A combination of these two approaches made it possible to prepare a series of previously inaccessible aminofurazans.

Experimental

The melting points were determined on a Kofler stage. The ^{1}H, ^{13}C, and ^{14}N NMR spectra were recorded on a Bruker AM-300 spectrometer operating at 300.13, 75.7, and 21.5 MHz, respectively, at natural isotope abundance. The chemical shifts in the ^{14}N NMR spectra are given in the δ scale relative to nitromethane as the external standard. The spin-spin coupling constants $^1J_{^{15}N,^1H}$ were measured using the INEPT technique. The mass spectra were obtained on Varian MAT CH-6 and Varian MAT CH-111 instruments (70 eV). The IR spectra were measured on a Specord IR-75 spectrometer (in KBr pellets for solids and in a thin layer for liquid samples). The course of the reactions and the purity of the products were monitored by TLC on Silufol UV-254 plates. Preparative chromatography was carried out with the use of silica gel.

Starting nitrofurazans **1**,[20] **17**,[20] **32**,[20] **35**,[20] **37**,[5] **39**,[20] **40**,[20] and **46** [20] and amidoxime **48** [9] were prepared according to known procedures. Amines were purchased from Aldrich.

X-ray diffraction study. X-ray diffraction data sets for compounds **3**, **29**, **53**, **57**, and **59a** were collected on a SMART CCD 1000 diffractometer at 110 K. The crystals of compound **38b** were studied on a Siemens P3/PC diffractometer at room temperature.

The structures were solved by direct methods and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. The hydrogen atoms were revealed from difference electron density maps and refined isotropically. All calculations were carried out using the SHELXTL PLUS program package.[21] The complete data of X-ray diffraction study were deposited with the Cambridge Structural Database (CSD).

Reactions of 3,4-dinitrofurazan (1) with amines (general procedures). *A*. A solution of compound **1** (10 mmol) in cold CH_2Cl_2 (15 mL) was added dropwise with stirring to a solution of alkylamine (30 mmol) in anhydrous CH_2Cl_2 (40—50 mL) at a temperature from −15 to −10 °C (a $CHCl_3$+carbon-dioxide ice bath). After completion of mixing of the reagents, cooling was terminated and the reaction mixture was allowed to warm to ~20 °C. The resulting mixture was successively washed with water (3×20 mL), 5% HCl (3×20 mL), and water (3×20 mL). The organic layer was dried with $MgSO_4$. After removal of the solvent, the product was crystallized or frozen out from a 1 : 1 CH_2Cl_2—pentane mixture (−15 °C).

B. The reaction was carried out analogously to the method *A* using a mixture of alkylamine (12 mmol) and Et_3N (20 mmol) in the reaction with compound **1** (10 mmol).

C. A solution of compound **1** (10 mmol) in $CHCl_3$ or CH_2Cl_2 (15—25 mL) was added with vigorous stirring to a solution of amine or its hydrochloride (12 mmol) and $NaHCO_3$ (20 mmol;

30 mmol in the reaction with amine hydrochloride) in water (15—25 mL) cooled to 0 °C. The reaction mixture was stirred at room temperature for 3 h. Then CH_2Cl_2 (50 mL) was added. The organic phase was separated and successively washed with water (3×20 mL), 5% HCl (3×20 mL), and water (3×20 mL). The organic layer was dried with calcined $MgSO_4$. The residue was worked up as described in the method *A*.

D. The reaction was carried out as described in the method *C* with the use of a mixture Na_2CO_3 (10 mmol; 15 mmol in the reaction with amine hydrochloride) and $Na_2S_2O_8$ (5 mmol) instead of $NaHCO_3$.

The yields and characteristics of the compounds synthesized are given in Tables 2—5.

3-Nitro-4-(*m*-tolylamino)furazan (13a) (general procedure). A solution of compound **1** (1.6 g, 10 mmol) in CCl_4 (25 mL) was slowly added dropwise to a solution of *m*-toluidine (3.87 g, 36 mmol) in CCl_4 (25 mL) at a temperature no higher than 0—1 °C. After mixing of the reagents, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and successively washed with ice water (3×50 mL), 5% HCl (3×20 mL), and water (3×50 mL). The organic extract was filtered through a thin layer of silica gel and dried with $CaCl_2$. After removal of the solvent, the residue was recrystallized from pentane and orange needle-like crystals were obtained in a yield of 1.61 g (73%).

3-Nitro-4-(*p*-tolylamino)furazan (13b) was prepared analogously from *p*-toluidine (1.14 g, 10.8 mmol) and compound **1** (0.6 g, 3.75 mmol) as orange crystals in a yield of 0.56 g (67.9%).

3-(1-Naphthylamino)-4-nitrofurazan (13c) was prepared analogously from 1-naphthylamine (0.72 g, 5 mmol) and compound **1** (0.32 g, 2 mmol) as small red-claret crystals in a yield of 0.29 g (56.7%).

1,3-Bis(3-aminofurazan-4-yl)triazene (15). A solution of compound **1** (1.6 g, 10 mmol) in MeCN (5 mL) was added dropwise to a suspension of 3,4-diaminofurazan (**14**) (1 g, 10 mmol) in MeCN (15 mL). The reaction mixture was heated to 40—50 °C until a homogeneous solution was obtained. Then the mixture was stirred at ~20 °C for 12 h and diluted with water (20—30 mL). The product was filtered off, washed with water, and dried in air. After recrystallization from Pr^iOH, pale-cream-colored crystals of **15** were prepared in a yield of 0.23 g (22%), m.p. 176—177 °C (with decomp.). Found (%): C, 22.66; H, 2.45; N, 59.57. $C_4H_5N_9O_2$ (211.14). Calculated (%): C, 22.75; H, 2.39; N, 59.70. IR (KBr), ν/cm^{-1}: 3480, 3460, 3356, 1636, 1604, 1564, 1508, 1492, 1452, 1436, 1416, 1340, 1292, 1244, 1012, 936, 872, 852. ^1H NMR (DMSO-d_6), δ: 6.30 (s, 4 H); 13.80—14.10 (s, 1 H). ^{13}C NMR (DMSO-d_6), δ: 149.2 (CN_3H), 150.7 (CNH_2). MS, *m/z*: 211 $[M]^+$, 100, 70.

3-Amino-4-nitrofurazan (17). A solution of amine **14** (0.35 g, 3.5 mmol) in anhydrous $MeO(CH_2)_2OMe$ (15 mL) was placed in a 50-mL three-neck flask equipped with a thermometer and two dropping funnels. Then a solution of Bu^nLi (0.22 g, 3.47 mmol, 0.0255 g mL^{-1}) in pentane was added dropwise with stirring at −35 °C under a static atmosphere of argon. The reaction mixture was stirred at −35 °C for 20 min and the temperature was raised to −10 °C. Then a solution of compound **1** (0.56 g, 3.5 mmol) in anhydrous $MeO(CH_2)_2OMe$ (10 mL) cooled to −15 °C was added dropwise. The reaction mixture was stirred at −10 °C for 30 min, after which cooling was terminated. The reaction mixture was allowed to warm to ~20 °C, stirred for 1 h, neutralized with 5% HCl, and concentrated on a rotary evaporator to 10 mL. Water (50 mL) was added to the residue and the mixture was extracted with CH_2Cl_2 (3×30 mL). The extract was dried with $MgSO_4$ and filtered through a small layer of silica gel. The solvent was evaporated. After recrystallization from $CHCl_3$, lemon-yellow crystals were obtained in a yield of 0.17 g (37%), m.p. 124—125 °C (*cf.* lit. data[5]: m.p. 124—125 °C). The spectroscopic characteristics are consistent with to the data published in the literature.

3-(3-Ethoxycarbonylpiperazin-1-yl)-4-nitrofurazan (28b). A solution of compound **1** (1.6 g, 10 mmol) in cold CH_2Cl_2 (10 mL) was added dropwise with stirring to a solution of ethoxycarbonylpiperazine (1.9 g, 12 mmol) and Et_3N (1.5 g, 15 mmol) in CH_2Cl_2 (20 mL) at a temperature from −15 to −10 °C. After completion of mixing of the reagents, cooling was terminated and the temperature of the reaction mixture was slowly raised to ~20 °C. The mixture was washed with water (3×20 mL). The organic layer was dried with $MgSO_4$ and filtered through a small layer of silica gel. The solvent was removed to obtain an oil, which gradually crystallized out. The yield and selected physicochemical data are given in Tables 3 and 4. IR (KBr), ν/cm^{-1}: 2988, 2932, 1680, 1584, 1484, 1460, 1432, 1300, 1284, 1248, 1204, 1128, 1080, 1028, 1020, 984, 908, 824. ^1H NMR ($CDCl_3$), δ: 1.22 (s, 3 H, Me); 3.31 and 3.61 (both br.s, 4 H each, NCH_2); 4.12 (s, 2 H, $C\underline{H}_2Me$). ^{13}C NMR ($CDCl_3$), δ: 14.4 (Me), 42.5 (NCH_2), 48.7 (NCH_2), 61.6 ($\underline{C}H_2Me$), 152.8 (C—N), 153.8 ($C—NO_2$), 155.0 (C=O). ^{14}N NMR ($CDCl_3$), δ: −33.5 (NO_2).

3-Nitro-4-(piperazin-1-yl)-furazan (28c). A mixture of compound **28b** (2.7 g, 10 mmol) and 20% $HClO_4$ (30 mL) was stirred at 70—80 °C for 48 h. After cooling, the reaction mixture was extracted with CH_2Cl_2 (2×30 mL) to remove unconsumed starting compound **28b**. The aqueous phase was treated with $NaHCO_3$ until it became alkaline and extracted with CH_2Cl_2 (2×30 mL). The organic layer was dried with $MgSO_4$. The solvent was removed to obtain an oil, which gradually crystallized out. The yield and selected physicochemical data are given in Tables 3 and 4. IR (KBr), ν/cm^{-1}: 2956, 2920, 2852, 2752, 1588, 1560, 1484, 1452, 1356, 1324, 1260, 1204, 1184, 1140, 1052, 1024, 1004, 876, 824. ^1H NMR ($CDCl_3$), δ: 2.93 (s, 4 H, NCH_2); 3.30 (s, 4 H, NCH_2). ^{13}C NMR ($CDCl_3$), δ: 44.7 (NCH_2), 48.7 (NCH_2), 152.7 (C—N), 153.7 ($C—NO_2$). ^{14}N NMR ($CDCl_3$), δ: −32.8 (NO_2).

3-(Indolizin-1-yl)-4-nitrofurazan (30). A solution of compound **1** (1.6 g, 10 mmol) in CH_2Cl_2 (10 mL) was slowly added dropwise with stirring to a solution of indolizine (1.43 g, 12 mmol) and Et_3N (1.21 g, 12 mmol) in CH_2Cl_2 (15 mL) at −5 °C. Then the temperature of the mixture was raised to ~20 °C and CH_2Cl_2 (20 mL) was added. The mixture was successively washed with water (2×15 mL), 5% HCl (2×15 mL), and water (2×20 mL). The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a column (SiO_2 40/100, a 2 : 1 CH_2Cl_2—pentane mixture as the eluent). Fraction 1, colorless product **30**, the yield was 0.56 g (24%), R_f 0.70, m.p. 117—118 °C. ^1H NMR ($CDCl_3$), δ: 3.30 (t, 2 H, $C\underline{H}_2Ar$, J = 7.5 Hz); 4.12 (t, 2 H, NCH_2, J = 7.5 Hz); 7.04—7.53 (m, 4 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 28.6 ($\underline{C}H_2Ar$), 50.2 (NCH_2), 113.9, 123.4, 125.0, 127.7 ($\underline{C}H$, Ph), 130.6 ($\underline{C}—CH_2$, Ph), 142.8 ($\underline{C}—N$, Ph), 146.7 (C—N), 153.8 ($C—NO_2$). ^{14}N NMR ($CDCl_3$), δ: −32.5 (NO_2). Fraction 2, *N*-nitrosoindolizine, the yield was 0.43 g (29%), R_f 0.4, m.p. 82.5—83 °C (*cf.* lit. data[22]: m.p. 83 °C). The spectroscopic characteristics are consistent with the data published in the literature.

4,4′-Dipyrrolidinobifurazan (34a). A solution of compound **32** (2.28 g, 10 mmol) in cold CH_2Cl_2 (15 mL) was added dropwise with stirring to a solution of pyrrolidine (4.16 g, 50 mmol) in anhydrous CH_2Cl_2 (40—50 mL) at a temperature from −15 to −10 °C. Then the temperature of the reaction mixture was slowly raised to ~20 °C. The reaction mixture was successively washed with water (3×20 mL), 5% HCl (3×20 mL), and water (3×20 mL). The organic layer was dried with $MgSO_4$. After removal of the solvent, the product was crystallized from hexane to obtain colorless crystals in a yield of 2.24 g (81%), m.p. 134—135 °C. Found (%): C, 52.24; H, 5.92; N, 30.37. $C_{12}H_{16}N_6O_2$ (276.30). Calculated (%): C, 52.17; H, 5.84; N, 30.42. IR (KBr), ν/cm^{-1}: 2960, 2880, 1688, 1592, 1480, 1460, 1248, 1184, 1160, 1132, 1112, 1024, 988, 904, 848. ^{1}H NMR ($CDCl_3$), δ: 1.93 (m, 8 H, $CH_2C\underline{H}_2CH_2$); 3.27 (m, 8 H, NCH_2). ^{13}C NMR ($CDCl_3$), δ: 25.4 ($CH_2\underline{C}H_2CH_2$), 49.2 (NCH_2), 135.5 (C—C), 156.5 (C—N). MS, *m/z*: 276 [M]$^+$, 246 [M − NO]$^+$, 216 [M − 2 NO]$^+$.

Compounds **34b—d** were prepared analogously.

4,4′-Dipiperidinobifurazan (34b). The yield was 95%, m.p. 94—95.5 °C (hexane). Found (%): C, 55.30; H, 6.71; N, 27.55. $C_{14}H_{20}N_6O_2$ (304.35). Calculated (%): C, 55.25; H, 6.62; N, 27.61. IR (KBr), ν/cm^{-1}: 3010, 2980, 1670, 1550, 1438, 1348, 1300, 1280, 1255, 1211, 1147, 1010, 980. ^{1}H NMR ($CDCl_3$), δ: 1.61 (m, 12 H, $CH_2C\underline{H}_2CH_2$); 3.15 (m, 8 H, NCH_2). ^{13}C NMR ($CDCl_3$), δ: 23.5 ($CH_2\underline{C}H_2CH_2$), 24.8 ($CH_2\underline{C}H_2CH_2$), 49.7 (NCH_2), 137.3 (C—C), 159.2 (C—N). MS, *m/z*: 304 [M]$^+$, 274 [M − NO]$^+$, 244 [M − 2 NO]$^+$.

4,4′-Dimorpholinobifurazan (34c). The yield was 91%, m.p. 145—146 °C (benzene). Found (%): C, 46.79; H, 5.31; N, 27.19. $C_{12}H_{16}N_6O_4$ (308.30). Calculated (%): C, 46.75; H, 5.23; N, 27.26. MS, *m/z*: 308 [M]$^+$, 278 [M − NO]$^+$, 248 [M − 2 NO]$^+$.

4,4′-Bis(tetrahydroisoquinolin-1-yl)bifurazan (34d). The yield was 75%, m.p. 153—155 °C (hexane). Found (%): C, 66.04; H, 5.11; N, 20.98. $C_{22}H_{20}N_6O_2$ (400.44). Calculated (%): C, 65.99; H, 5.03; N, 20.99. IR (KBr), ν/cm^{-1}: 3424, 3016, 2936, 1688, 1548, 1456, 1376, 1344, 1304, 1272, 1256, 1232, 1216, 1152, 1120, 1088, 1048, 984. ^{1}H NMR ($CDCl_3$), δ: 2.92 (t, 4 H, $NCH_2C\underline{H}_2$Ar, *J* = 6.1 Hz); 3.52 (t, 4 H, $NC\underline{H}_2CH_2$Ar, *J* = 6.1 Hz); 4.51 (s, 4 H, $NC\underline{H}_2$Ar); 7.15—7.34 (m, 8 H, Ar). ^{13}C NMR ($CDCl_3$), δ: 27.8, 46.6, 50.5, 126.3, 126.8, 128.8, 132.1, 133.3, 137.1 (C—C), 158.7 (C—N). MS, *m/z*: 400 [M]$^+$, 370 [M − NO]$^+$, 340 [M − 2 NO]$^+$.

4-Morpholino-4′-nitrobifurazan (33). The yield was 15%, m.p. 110—112 °C (CCl_4). Found (%): C, 35.94; H, 3.07; N, 31.28. $C_8H_8N_6O_5$ (268.19). Calculated (%): C, 35.83; H, 3.01; N, 31.34. MS, *m/z*: 268 [M]$^+$, 238 [M − NO]$^+$, 222 [M − NO_2]$^+$, 208 [M − 2 NO]$^+$. ^{14}N NMR ($CDCl_3$), δ: −39.4 (NO_2).

4,4′-Dipiperidinoazofurazan (36b). A solution of 4,4′-dinitroazofurazan (**30**) (1.28 g, 5 mmol) in CH_2Cl_2 (20 mL) was slowly added dropwise to a solution of piperidine (2.13 g, 25 mmol) in CH_2Cl_2 (15 mL) at 0—5 °C. The resulting dark-claret reaction mixture was successively washed with water (2×25 mL), 5% HCl (2×15 mL), and water (2×25 mL). The organic layer was dried over $MgSO_4$ and the solvent was evaporated in *vacuo*. The residue was recrystallized from hexane. A dark-claret crystalline product was obtained in a yield of 1.54 g (93%), m.p. 116—117 °C. Found (%): C, 50.61; H, 6.06; N, 33.67. $C_{14}H_{20}N_8O_2$ (332.27). Calculated (%): C, 50.59; H, 6.07; N, 33.71. IR (KBr), ν/cm^{-1}: 2952, 2880, 1560, 1472, 1388, 1256, 1148, 1136, 1056, 1044, 1024, 936, 924, 856. ^{1}H NMR ($CDCl_3$), δ: 1.72 (m, 12 H, $CH_2C\underline{H}_2C\underline{H}_2CH_2$); 3.58 (m, 8 H, NCH_2). ^{13}C NMR ($CDCl_3$), δ: 23.9, 25.0, 49.3, 156.4 ($\underline{C}$—NCH_2), 157.0 (CN=N). MS, *m/z*: 332 [M]$^+$, 302 [M − NO]$^+$, 272 [M − 2 NO]$^+$.

4,4-Dimorpholinoazofurazan (36c) was prepared analogously to compound **36b**. The yield was 88%, m.p. 194—195 °C (EtOH). Found (%): C, 42.95; H, 4.92; N, 33.21. $C_{12}H_{16}N_8O_4$ (336.31). Calculated (%): C, 42.86; H, 4.80; N, 33.32. MS, *m/z*: 336 [M]$^+$, 306 [M − NO]$^+$.

4-Amino-4′-piperidinoazofurazan (38a). Solid compound **37** (2.26 g, 10 mmol) was slowly added with stirring to a solution of piperidine (2.13 g, 25 mmol) in DMSO (8 mL) at ~20 °C. The resulting dark-claret reaction mixture was stirred for 20 min and diluted with water (50 mL). The precipitate that formed was filtered off, washed with water, and dried in air. After recrystallization from Pr^iOH, the product was obtained in a yield of 2.08 g (79%), m.p. 142—144 °C. Found (%): C, 41.01; H, 4.62; N, 42.29. $C_9H_{12}N_8O_2$ (264.25). Calculated (%): C, 40.91; H, 4.58; N, 42.40. IR (KBr), ν/cm^{-1}: 3472, 3376, 3048, 2880, 1612, 1600, 1480, 1420, 1390, 1190, 940. ^{1}H NMR (DMSO-d_6), δ: 6.89 (s, 2 H, NH_2). MS, *m/z*: 264 [M]$^+$, 234 [M − NO]$^+$.

Compounds **38b** and **38c** were prepared analogously.

4-Amino-4′-morpholinoazofurazan (38b). The yield was 81%, m.p. 131—132 °C. Found (%): C, 36.17; H, 3.84; N, 41.97. $C_8H_{10}N_8O_3$ (266.22). Calculated (%): C, 36.09; H, 3.79; N, 42.09. MS, *m/z*: 264 [M]$^+$, 234 [M − NO]$^+$.

4-Amino-4′-(dibutylamino)azofurazan (38c). The yield was 78%, m.p. 185—186 °C. Found (%): C, 46.79; H, 6.58; N, 36.21. $C_{12}H_{20}N_8O_2$ (308.34). Calculated (%): C, 46.74; H, 6.54; N, 36.34. MS, *m/z*: 308 [M]$^+$, 278 [M − NO]$^+$. ^{1}H NMR (DMSO-d_6), δ: 6.89 (s, 2 H, NH_2).

3-Amino-4-(piperidin-1-yl)furazan (41). *A*. A solution of compound **17** (1.3 g, 10 mmol) in piperidine (5 mL) was refluxed under a static atmosphere of argon for 5 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and successively washed with water (3×30 mL), 10% HCl (2×20 mL), and water (20 mL). The organic layer was dried with $MgSO_4$ and concentrated. The residue was recrystallized from MeOH. The product was obtained in a yield of 0.57 g (34%), m.p. 92—94 °C (*cf*. lit. data[23]: m.p. 93 °C).

B. Compound **14** (1 g, 10 mmol) and piperidine (5 mL) were placed in an autoclave and the mixture was stirred at 150—160 °C for 1 h. After cooling, the reaction mixture was worked up as described in the method *A*. The product was obtained in a yield of 0.13 g (8%), m.p. 91—93 °C.

Compounds **42** and **43a—c** were prepared analogously.

3-(4-Methylpiperazin-1-yl)-4-phenylfurazan oxalate (42). The yield was 35%, m.p. 223—226 °C. Found (%): C, 54.01; H, 5.68; N, 16.62. $C_{15}H_{18}N_4O_5$ (334.33). Calculated (%): C, 53.89; H, 5.43; N, 16.76. IR (KBr), ν/cm^{-1}: 3032, 2864, 1724, 1664, 1584, 1568, 1528, 1480, 1464, 1400, 1268, 1180, 1100, 1068, 988, 928, 888. ^{1}H NMR (DMSO-d_6), δ: 2.67 (s, 3 H, Me); 3.13, 3.31 (m, 8 H, CH_2); 6.35 (br.s, 1 H, OH); 7.58, 7.77 (m, 5 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 42.7 (Me), 46.3, 51.4 (CH_2), 125.5, 127.7, 129.3, 130.9 (Ph); 147.7 ($\underline{C}$—Ph), 158.0 (CN), 164.2 (CO). MS, *m/z*: 244 [M]$^+$, 214 [M − NO]$^+$.

3-(4-Methylpiperazin-1-yl)-4-methylfurazan oxalate (43a). The yield was 32%, m.p. 162—164 °C. Found (%): C, 44.27; H, 6.13; N, 20.46. $C_{10}H_{16}N_4O_5$ (272.26). Calculated (%):

C, 44.12; H, 5.92; N, 20.58. IR (KBr), ν/cm^{-1}: 3008, 2968, 2544, 2328, 1720, 1696, 1584, 1520, 1464, 1404, 1272, 1248, 1192, 1064, 1032, 984. ^{1}H NMR (DMSO-d_6), δ: 2.30 and 2.57 (both s, 3 H each, Me); 3.14—3.45 (m, 8 H, CH_2); 5.83 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 9.6 (C—Me), 42.7 (N—Me), 45.5, 51.6 (CH_2), 145.4 (C—Me), 158.7 (C—N), 164.5 (CO). MS, *m/z*: 182 $[M]^+$, 152 $[M - NO]^+$.

3-Methyl-4-(piperazin-1-yl)furazan hydrochloride (43b). The yield was 9%, m.p. 171—172 °C (from Pr^{i}OH). Found (%): C, 41.13; H, 6.43; N, 27.26. $C_7Cl_1H_{13}N_4O_1$ (204.66). Calculated (%): C, 41.08; H, 6.40; N, 27.38. IR (KBr), ν/cm^{-1}: 2940, 2700, 2605, 2475, 2448, 1584, 1460, 1400, 1256, 1240, 1148, 1088, 1032, 980, 916. ^{1}H NMR (DMSO-d_6), δ: 2.35 (s, 3 H, Me); 3.22—3.45 (m, 8 H, CH_2); 4.02 (br.s, OH+HCl). ^{13}C NMR (DMSO-d_6), δ: 9.6 (C—Me), 42.0 (CH_2—NH), 45.0 (CH_2—N—C), 145.6 (C—Me), 158.9 (N=C—N). MS, *m/z*: 168 $[M]^+$, 138 $[M - NO]^+$.

3-Methyl-4-morpholinofurazan (43c). The yield was 41%, m.p. 61.5—63 °C (hexane). Found (%): C, 49.77; H, 6.60; N, 24.76. $C_7H_{11}N_3O_2$ (169.18). Calculated (%): C, 49.70; H, 6.55; N, 24.84. MS, *m/z*: 169 $[M]^+$, 139 $[M - NO]^+$.

4-Benzylamino-3-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)furazan (47a). A solution of compound **46** (2.51 g, 10 mmol) in CH_2Cl_2 (10 mL) was slowly added dropwise with stirring to a solution of benzylamine (2.67 g, 25 mmol) in MeCN (10 mL) at 0—5 °C. The reaction mixture was stirred for 10 h, diluted with CH_2Cl_2 (50 mL), and washed successively with water (4×25 mL), 5% HCl (2×15 mL), and water (2×25 mL). The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (100—160 μm, a 1 : 1 CH_2Cl_2—pentane mixture as the eluent). After recrystallization from hexane, the colorless product was obtained in a yield of 1 g (32%), m.p. 89—91 °C. Found (%): C, 46.36; H, 2.62; N, 22.41. $C_{12}H_8F_3N_5O_2$ (311.22). Calculated (%): C, 46.31; H, 2.59; N, 22.50. IR (KBr), ν/cm^{-1}: 3406, 2916, 2867, 1621, 1520, 1453, 1400, 1376, 1356, 1344, 1324, 1240, 1096, 1028, 1000, 983. ^{1}H NMR ($CDCl_3$), δ: 4.55 (d, 2 H, CH_2, J = 5.6 Hz); 6.60 (br.s, 1 H, NH); 7.25—7.45 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 44.0 (CH_2), 115.6 (CF_3), 127.9, 128.2, 128.9, 135.8 (C_i), 137.4 (N—C=N), 148.9 (C—C—C), 155.6 (C—N), 157.6 (C—CF_3). ^{19}F NMR ($CDCl_3$), δ: −74.9. MS, *m/z*: 311 $[M]^+$, 281 $[M - NO]^+$.

4-Morpholino-3-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)furazan (47b) was prepared analogously to compound **47a**. The yield was 30%, m.p. 129—131 °C (hexane). Found (%): C, 37.20; H, 2.80; N, 23.97. $C_9H_8F_3N_5O_3$ (291.19). Calculated (%): C, 37.12; H, 2.77; N, 24.05. MS, *m/z*: 291 $[M]^+$, 261 $[M - NO]^+$.

4-Morpholino-3-(5-trichloromethyl-1,2,4-oxadiazol-3-yl)furazan (49). A mixture of 4-morpholinofurazan-3-carbohydroximoamide (**48**) (2.13 g, 10 mmol) and trichloroacetyl chloride (3.64 g, 20 mmol) was heated at 130—140 °C for 40 min and then cooled. The product was stirred with a saturated $NaHCO_3$ solution (40 mL). After 2 h, the precipitate was filtered off, washed with water, and crystallized from Et_2O. The product was obtained in a yield of 2.79 g (82%), m.p. 70—72 °C. Found (%): C, 31.70; H, 2.36; N, 20.47. $C_9H_8Cl_3N_5O_3$ (340.55). Calculated (%): C, 31.74; H, 2.37; N, 20.56.

4-Morpholino-3-(5-piperidino-1,2,4-oxadiazol-3-yl)furazan (50c). A solution of compound **49** (1.7 g, 5 mmol) and piperidine (0.85 g, 10 mmol) in anhydrous THF (10 mL) was refluxed for 12 min. The reaction mixture was concentrated *in vacuo*. The residue was washed with water and crystallized from 95% EtOH. The product was obtained in a yield of 1.17 g (66%), m.p. 91—93 °C. Found (%): C, 51.02; H, 6.00; N, 27.35. $C_{13}H_{18}N_6O_3$ (306.32). Calculated (%): C, 50.97; H, 5.92; N, 27.44.

Compounds **50a,b** and **51** were prepared analogously.

3-(5-Benzylamino-1,2,4-oxadiazol-3-yl)-4-morpholinofurazan (50a). The yield was 70%, m.p. 162—164 °C. Found (%): C, 54.92; H, 4.94; N, 25.55. $C_{15}H_{16}N_6O_3$ (328.33). Calculated (%): C, 54.87; H, 4.91; N, 25.60.

3-{5-[2-(Dimethylamino)ethylamino]-1,2,4-oxadiazol-3-yl}-4-morpholinofurazan (50b). The yield was 76%, m.p. 142—143 °C. Found (%): C, 46.44; H, 6.16; N, 31.59. $C_{12}H_{19}N_7O_3$ (309.33). Calculated (%): C, 46.40; H, 6.19; N, 31.70.

3-(4-Morpholinofurazan-3-yl)[1,2,4]oxadiazol-3(4*H*)-one (51). A solution of compound **49** (1.7 g, 5 mmol) in 10% aqueous NaOH (15 mL) was kept for 30 min. The reaction mixture was acidified with concentrated HCl to pH 2. The precipitate that formed was filtered off, washed with water, and recrystallized from 95% EtOH. The product was obtained in a yield of 1.03 g (86%), m.p. 253—255 °C. Found (%): C, 40.19; H, 3.85; N, 29.19. $C_8H_9N_5O_4$ (239.19). Calculated (%): C, 40.17; H, 3.79; N, 29.28.

***O*-(4-Methylfurazan-3-ylcarbonyl)-4-morpholinofurazan-3-carbohydroximoamide (52).** 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.11 g, 11 mmol) was added to a solution of compound **48** (2.13 g, 10 mmol) and 4-methylfurazan-3-carboxylic acid[24] (1.28 g, 10 mmol) in anhydrous THF (15 mL). The reaction mixture was stirred for 30 min. The solvent was removed *in vacuo*. The residue was washed with water and recrystallized from 95% EtOH. The product was obtained in a yield of 2.71 g (84%), m.p. 145—147 °C. Found (%): C, 40.94; H, 4.10; N, 30.21. $C_{11}H_{13}N_7O_5$ (323.27). Calculated (%): C, 40.87; H, 4.05; N, 30.33. IR (KBr), ν/cm^{-1}: 3422, 3310, 3182, 1760, 1650, 1611, 1506, 1520, 1278, 1265, 1190, 1110, 1070, 1055, 1039, 1012, 925, 906, 842, 775. ^{1}H NMR (acetone-d_6), δ: 2.56 (s, 3 H, CH_3); 3.38 and 3.73 (both t, 4 H each, CH_2, J = 4.5 Hz); 7.69 (br.s, 2 H, NH_2).

3-{4-[5-(4-Methylfurazan-3-yl)[1,2,4]oxadiazol-3-yl]}-4-morpholinofurazan (53). A solution of compound **52** (1.62 g, 5 mmol) in DMF (10 mL) was refluxed for 6 min. The reaction mixture was cooled and diluted with water (50 mL). The precipitate that formed was filtered off and recrystallized from CCl_4. Compound **53** was prepared in a yield of 1.34 g (88%), m.p. 101—103 °C. Found (%): C, 43.33; H, 3.65; N, 32.08. $C_{11}H_{11}N_7O_4$ (305.25). Calculated (%): C, 43.28; H, 3.63; N, 32.12.

4-Morpholinofurazan-3-carbohydroxymoyl chloride (54). A solution of $NaNO_2$ (1.04 g, 15 mmol) in water (5 mL) was added dropwise to a solution of compound **48** (2.13 g, 10 mmol) in 6 *M* HCl (20 mL) at 5—10 °C. The reaction mixture was stirred for 2 h. The precipitate was filtered off and washed with water. Compound **54** was obtained in a yield of 2.05 g (88%), m.p. 165—167 °C. Found (%): C, 36.20; H, 3.86; N, 24.06. $C_7H_9Cl_1N_4O_3$ (232.63). Calculated (%): C, 36.14; H, 3.90; N, 24.08. IR (KBr), ν/cm^{-1}: 3142, 1640, 1562, 1521, 1310, 1260, 1109, 1066, 1035, 1010, 942, 891, 880, 850, 842, 800. ^{1}H NMR (acetone-d_6), δ: 3.43 and 3.69 (both t, 4 H each, CH_2, J = 4.4 Hz); 12.05 (s, 1 H, OH).

4-Piperidinofurazan-3-carbohydroxymoyl chloride, was prepared analogously, the yield was 84%, m.p. 127—129 °C. Found (%): C, 41.71; H, 4.83; N, 24.24. $C_8H_{11}Cl_1N_4O_2$ (230.65). Calculated (%): C, 41.66; H, 4.81; N, 24.29. IR (KBr), ν/cm^{-1}: 3140, 1611, 1495, 1400, 1310, 1270, 1258, 1205, 1141, 1092, 1071, 1052, 1039, 1025, 1004, 940, 915, 885, 864, 780, 699. ^{1}H NMR (acetone-d_6), δ: 1.61 (s, 6 H, CH_2); 3.14 (m, 4 H, CH_2).

***N´*-Benzylfurazan-4-morpholino-3-carbohydroximoamide (55a).** A solution of compound **54** (2.32 g, 10 mmol) in MeCN (15 mL) was added dropwise to a solution of $BnNH_2$ (1.61 g, 15 mmol) and Et_3N (1.52 g, 15 mmol) in MeCN (20 mL) at 5—10 °C. The reaction mixture was stirred for 2 h and the solvent was removed *in vacuo*. Water (20 mL) was added to the residue and the product was extracted with Et_2O (3×20 mL). The extract was dried with Na_2SO_4, the solvent was evaporated, and the product was recrystallized from Et_2O. The yield was 2.45 g (81%), m.p. 119—121 °C. Found (%): C, 55.51; H, 5.69; N, 23.12. $C_{14}H_{17}N_5O_3$ (303.32). Calculated (%): C, 55.44; H, 5.65; N, 23.09.

Compounds **55b** and **55c** were prepared analogously.

***E*-4-Morpholinofurazan-3-carbohydroxymoylpyrrolidine (55b).** The yield was 82%, m.p. 164—165 °C (95% EtOH). Found (%): C, 49.45; H, 6.44; N, 26.14. $C_{11}H_{17}N_5O_3$ (267.29). Calculated (%): C, 49.43; H, 6.41; N, 26.20.

***N´*-(4-Methoxyphenyl)furazan-4-morpholino-3-carbohydroximoamide (55c).** The yield was 74%, m.p. 155—157 °C (95% EtOH). Found (%): C, 52.72; H, 5.40; N, 21.84. $C_{14}H_{17}N_5O_4$ (319.32). Calculated (%): C, 52.66; H, 5.37; N, 21.93.

4-Morpholinofurazan-3-carbohydroxymoyl azide (56). A solution of compound **54** (2.32 g, 10 mmol) in acetone (15 mL) was added dropwise to a solution of NaN_3 (1.95 g, 30 mmol) in a mixture of water (10 mL) and acetone (10 mL) at 5—10 °C. The reaction mixture was stirred for 2 h and the acetone was evaporated *in vacuo*. The precipitate was filtered off, dried in air, and recrystallized from Et_2O. The product was obtained in a yield of 1.46 g (62%), m.p. 130—132 °C. Found (%): C, 35.12; H, 3.76; N, 40.92. $C_7H_9N_7O_3$ (239.19). Calculated (%): C, 35.15; H, 3.79; N, 40.99.

1-Hydroxy-5-(4-morpholinofurazan-3-yl)tetrazole (57). A solution of compound **56** (1.2 g, 5 mmol) in Et_2O (30 mL) was saturated with dry HCl at 0 °C and kept for 16 h. The precipitate that formed was filtered off and recrystallized from 95% EtOH. Crystals were obtained in a yield of 1.03 g (86%), m.p. 216—218 °C. Found (%): C, 35.18; H, 3.75; N, 40.90. $C_7H_9N_7O_3$ (239.19). Calculated (%): C, 35.15; H, 3.79; N, 40.99. MS, *m/z*: 239 $[M]^+$, 211 $[M - N_2]^+$, 209 $[M - NO]^+$, 181 $[M - N_2 - NO]^+$

3-[(5-Methoxycarbonyl)-4,5-dihydroisoxazol-3-yl]-4-morpholinofurazan (58). A solution of compound **54** (1.16 g, 5 mmol) in diethyl ether (15 mL) was added dropwise to a solution of methyl acrylate (0.86 g, 10 mmol) and Et_3N (1.01 g, 10 mmol) in diethyl ether (10 mL) at 5—10 °C. The reaction mixture was stirred for 30 min, the solvent was evaporated *in vacuo*, and water (20 mL) was added to the residue. The product was filtered off, washed with water, and recrystallized from Et_2O. The colorless product was obtained in a yield of 0.90 g (64%), m.p. 109—111 °C. Found (%): C, 46.84; H, 5.02; N, 19.82. $C_{11}H_{14}N_4O_5$ (282.26). Calculated (%): C, 46.81; H, 5.00; N, 19.85.

The reaction with ethyl propiolate was carried out analogously. According to the results of ^{1}H NMR spectroscopy, the product was a mixture of isomers **59a** and **59b** in a ratio of 3 : 2. **3-[(5-Ethoxycarbonyl)isoxazol-3-yl]-4-morpholinofurazan (59a).** ^{1}H NMR (acetone-d_6), δ: 1.33 (t, 3 H, CH_3, J = 7.4 Hz); 3.27 and 3.76 (both t, 4 H each, CH_2, J = 4.3 Hz); 4.44 (q, 2 H, CH_2, J = 7.4 Hz); 7.69 (s, 1 H, CH). **3-[(4-Ethoxycarbonyl)isoxazol-3-yl]-4-morpholinofurazan (59b).** ^{1}H NMR (acetone-d_6), δ: 1.16 (t, 3 H, CH_3, J = 7.3 Hz); 3.06 and 3.57 (both t, 4 H each, CH_2, J = 4.3 Hz); 4.23 (q, 2 H, CH_2, J = 7.3 Hz); 9.98 (s, 1 H, CH). The product was twice recrystallized from an Et_2O—light petroleum mixture to prepare pure isomer **59a** in 32% yield, m.p. 130—132 °C. Found (%): C, 49.01; H, 4.81; N, 19.00. $C_{12}H_{14}N_4O_5$ (294.27). Calculated (%): C, 48.98; H, 4.80; N, 19.04.

3,4-Di(4-morpholinofurazan-3-yl)furoxan (60a). A solution of compound **63** (2.13 g, 10 mmol) in Et_2O (20 mL) was stirred with a 10% $NaHCO_3$ solution (30 mL) for 4 h. The reaction mixture was filtered. The ethereal layer was separated and dried with Na_2SO_4. The solvent was evaporated, light petroleum was added to the residue, and the precipitate that formed was filtered off. After recrystallization from $CHCl_3$, furoxan **60a** was obtained in a yield of 1.37 g (70%), m.p. 118—120 °C. Found (%): C, 42.90; H, 4.14; N, 28.48. $C_{14}H_{16}N_8O_6$ (392.33). Calculated (%): C, 42.86; H, 4.11; N, 28.56. MS, *m/z*: 392 $[M]^+$, 376 $[M - O]^+$, 362 $[M - NO]^+$. ^{1}H NMR (DMSO-d_6), δ: 6.89 (s, 4 H, NH_2).

Compounds **60b—d** were prepared analogously.

3,4-Di(4-piperidinofurazan-3-yl)furoxan (60b), the yield was 73%, m.p. 82—84 °C (Et_2O—light petroleum, 1 : 1). Found (%): C, 49.52; H, 5.20; N, 28.80. $C_{16}H_{20}N_8O_4$ (388.39). Calculated (%): C, 49.48; H, 5.19; N, 28.85. IR (KBr), ν/cm^{-1}: 1629, 1592, 1547, 1286, 1272, 1226, 1110, 1012, 992, 965, 900, 862, 808, 718. ^{1}H NMR (acetone-d_6), δ: 1.43 (br.s, 12 H, CH_2); 2.86—3.29 (m, 8 H, CH_2N). MS, *m/z*: 388 $[M]^+$, 372 $[M - O]^+$, 358 $[M - NO]^+$.

3,4-Di[4-(4-fluorophenyl)piperazinofurazan-3-yl]furoxan (60c), the yield was 71%, m.p. 150—152 °C (Et_2O). Found (%): C, 54.03; H, 4.16; N, 24.15. $C_{26}H_{24}F_2N_{10}O_4$ (578.54). Calculated (%): C, 53.98; H, 4.18; N, 24.21. IR (KBr), ν/cm^{-1}: 1624, 1550, 1510, 1235, 1211, 1150, 1022, 992, 968, 941, 838, 720. ^{1}H NMR (DMSO-d_6), δ: 3.03 and 3.31 (both br.s, 8 H each, CH_2); 6.96—7.20 (m, 8 H, C_6H_4). ^{13}C NMR (DMSO-d_6), δ: 48.4, 48.9 (NCH_2), 105.0 (CN→O), 115.3, 115.7, 117.7, 117.9 (CH), 134.4, 138.0, 144.7 (<u>C</u>—C), 147.5 (<u>C</u>—N, Ar), 156.5 (<u>C</u>—F, Ar), 158.9, 159.2 (C—N). MS, *m/z*: 578 $[M]^+$, 562 $[M - O]^+$, 548 $[M - NO]^+$.

3,4-Di[4-(1,2,3,4-tetrahydroisoquinolin-2-yl)furazan-3-yl]furoxan (60d), the yield was 62%, m.p. 54—56 °C (Et_2O). Found (%): C, 59.52; H, 4.21; N, 23.05. $C_{24}H_{20}N_8O_4$ (484.47). Calculated (%): C, 59.50; H, 4.16; N, 23.13. IR (KBr), ν/cm^{-1}: 1639, 1591, 1575, 1556, 1305, 1280, 1211, 1146, 1032, 992, 964, 931, 876, 808, 760, 750. ^{1}H NMR (DMSO-d_6), δ: 2.74, 2.85, 3.41, and 3.57 (all t, 2 H each, CH_2, J = 5.4 Hz); 4.34 and 4.44 (both s, 2 H each, CH_2); 7.14 (m, 8 H, Ar). ^{13}C NMR (DMSO-d_6), δ: 27.2, 27.4 ($NCH_2\underline{C}H_2Ar$), 45.6, 46.5 ($N\underline{C}H_2CH_2Ar$), 49.3, 50.3 ($N\underline{C}H_2Ar$), 105.5 (CN→O), 125.0, 126.4, 126.5, 126.6, 128.5, 128.6, 132.1, 132.5 (CH), 133.2, 133.4, 137.2, 145.6 (<u>C</u>—C), 158.2 (C—N). MS, *m/z*: 484 $[M]^+$, 468 $[M - O]^+$, 454 $[M - NO]^+$.

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