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Synthesis of new pharmacologically oriented heterocyclic ensembles, [2-(1*H*-pyrazol-1-yl)thiazol-4-yl]furoxans

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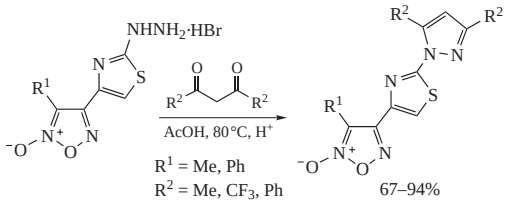
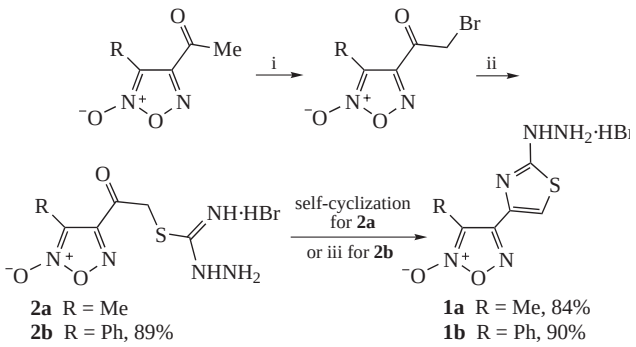
The effective synthesis of pharmacologically oriented heterocyclic ensembles, [2-(1*H*-pyrazol-1-yl)thiazol-4-yl]furoxans, comprising furoxan moiety as NO-donor and pharmacophoric pyrazolylthiazole fragment is based on the condensation of (2-hydrazinylthiazol-4-yl)furoxan hydrobromides with linear 1,3-diketones. The reaction proceeds through hydroxypyrazoline intermediate.



Nitrogen-containing heterocycles are among the most significant structural components of multitude pharmaceuticals.[1] Furoxans (1,2,5-oxadiazole 2-oxides) have attracted attention in recent decades owing to their ability to release NO under physiological conditions.[2] Our latest studies in the furoxan chemistry[3] were directed towards the construction of potential drug candidates, new hybrid structures containing furoxan motif as NO-donor linked to various pharmacophoric nitrogen-containing heterocycles.[4] Recently, the cytotoxic activity against five human cancer cell lines was revealed for a series of the synthesized hybrid structures.[5] One of the prospective heterocyclic frameworks for new furoxan-containing hybrid structures seems to be pyrazolylthiazole whose representatives are effective in treatment of cardiovascular diseases as selective inhibitors of fibrinogen-mediated platelet aggregation,[6] they display antinociceptive[7] and antibacterial activities against gram-positive and gram-negative bacteria,[8] and are toxic against *Candida elegans*.[9]

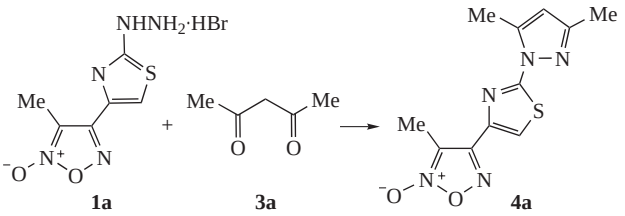
Recently,[10] we have synthesized promising 4-(2-hydrazinylthiazol-4-yl)-3-methylfuroxan hydrobromide **1a** and some its analogues by the reaction of the corresponding bromoacetylfuroxans with thiosemicarbazide under mild conditions (Scheme 1). Obviously, hydrazine moiety can be regarded as a backbone for the construction of pyrazole cycle, and compounds of type **1a** can be converted into conjugates comprising valuable furoxan, thiazole and pyrazole cores. The specific goal of this work was the synthesis of new hybrids bearing the NO-donor furoxan and the pyrazolylthiazole moieties.

To extend a set of initial compounds, we prepared 4-(2-hydrazinylthiazol-4-yl)-3-phenylfuroxan hydrobromide **1b** on the basis of 4-acetyl-3-phenylfuroxan as the starting material. Since this ketone was described many years ago[16] without experimental details and spectral characteristics, herein we renewed and improved its synthesis (Scheme S1, see Online Supplementary Materials). Its acetyl group was brominated, and the bromoacetyl derivative obtained was condensed with thiosemicarbazide, however, instead of expected compound **1b** its acyclic precursor **2b** was obtained. The cyclization of the latter into required thiazolylfuroxan **1b** was accomplished by heating in AcOH (see Scheme 1). Compound **1b** was characterized as the hydrazone with 4-nitrobenzaldehyde (see Online Supplementary Materials).



Scheme 1 *Reagents and conditions*: i, Br_2 (1 equiv.), AcOH, 47% HBr, 50 °C, 1.5 h; ii, $H_2NC(=S)NHNH_2$ (1 equiv.), MeCN, 20 °C, 4–12 h; iii, AcOH, 80 °C, 7 h.

Pyrazolylthiazoles are regularly obtained by the condensation of 2-hydrazinylthiazoles with 1,3-dicarbonyl compounds in polar solvents (EtOH, MeOH, AcOH) under acid catalysis. The outcome of this reaction is substrate- and acid-dependent, for instance, heating of 2-hydrazinyl-4-phenylthiazole with acetylacetone or dibenzoylmethane in the presence of AcOH gives fused bicyclic thiazolo[2,3-*c*][1,2,4]triazepine derivatives.[11,12] However, target pyrazolylthiazole is smoothly formed from 2-hydrazinyl-4-phenylthiazole and acetylacetone upon refluxing in MeOH with TsOH as the catalyst.[13] Pyrazolylthiazoles are formed as single products in the reaction of hydrazinylbenzothiazoles with acetylacetone and HCl as the catalyst.[14] A higher temperature is required for the reaction of aryl(hydrazinyl)thiazoles bearing electron-withdrawing substituents in the aromatic ring.[15] In this work, the search for optimal conditions for the formation of pyrazolylthiazole system from hydrazines of type **1** was performed with compound **1a** and acetylacetone **3a** as the model substrates (Scheme 2, Table 1).

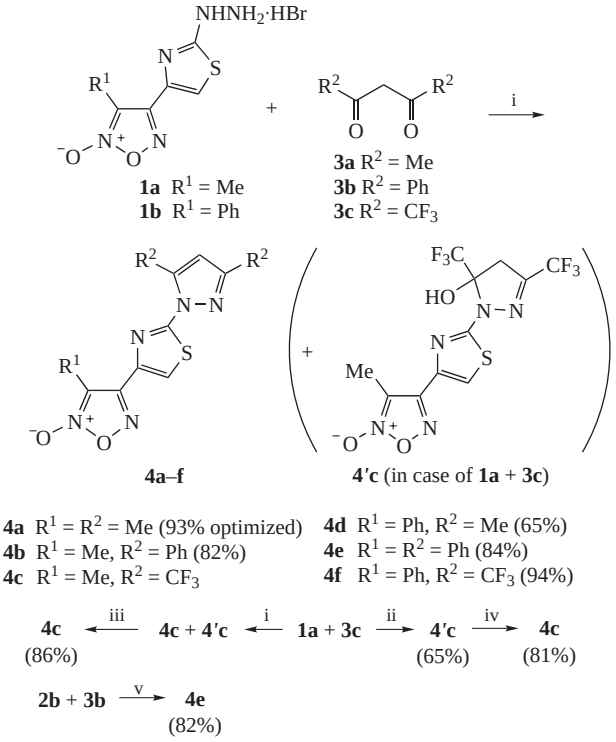


Scheme 2

Table 1 Optimization of the reaction conditions for the synthesis of compound **4a**.[a]

Entry	Solvent	Catalyst	*T*/°C	*t*/h	Yield of **4a** (%)
1	AcOH	–	20	72	11
2	AcOH	HCl (0.25 equiv.)	20	72	70
3	AcOH	HCl (1 equiv.)	20	24	71
4	AcOH	HCl (2 equiv.)	20	24	71
5	AcOH	–	80	10	35
6	AcOH	HCl (0.25 equiv.)	80	2	43
7	AcOH	HCl (0.25 equiv.)	80	4	64
8	AcOH	HCl (0.25 equiv.)	80	10	83
9	AcOH	H_2SO_4 (0.35 equiv.)	80	6	93
10	EtOH	–	20	72	7
11	EtOH	–	80	10	0
12	EtOH	HCl (0.25 equiv.)	80	6	71
13	EtOH	H_2SO_4 (0.35 equiv.)	80	10	87

[a] Molar ratio **1a**/**3a** of 1 : 2, solvent 4 ml per 1 mmol of **1a**.



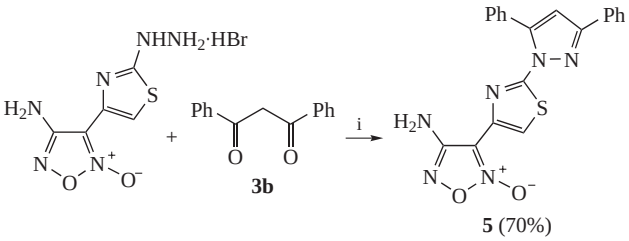
Scheme 3 *Reagents and conditions*: i, AcOH, 0.35 equiv. H_2SO_4, 80 °C, 6 h; ii, EtOH, 0.35 equiv. H_2SO_4, 80 °C, 5 h; iii, AcOH, 0.35 equiv. H_2SO_4, 80 °C, 11 h; iv, AcOH, 1.0 equiv. H_2SO_4, 80 °C, 5 h; v, AcOH, 0.35 equiv. H_2SO_4, 80 °C, 6 h. Molar ratios: **1** : **3a**,**c** = 1 : 2, **1** : **3b** = 1 : 1.4.

Since the initial compound **1a** contained latent HBr acid, the first attempts to obtain the target compound **4a** were made without additional catalyst in AcOH or EtOH at 20 °C for 72 h or at 80 °C for 10 h. The yields in these cases in AcOH were 35 and 11%, respectively (see Table 1, entries 1 and 5). Compound **4a** was practically not formed in EtOH without catalyst additives (entries 10 and 11). Using HCl as the catalyst (0.25 equiv.) enabled to obtain good results in both solvents and at both temperatures (entries 2–4, 6–8, 12). The maximum yields were achieved with H_2SO_4 (0.35 equiv.) (entries 9 and 13).

The optimal conditions for the preparation of compound **4a** were extended for the reaction of hydrazine derivatives **1a**,**b** with three 1,3-dicarbonyl compounds **3a**–**c** (Scheme 3).† The expected [2-(1*H*-pyrazol-1-yl)thiazol-4-yl]furoxans **4a**–**e** were obtained in all cases, however, the target structure **4c** was formed in the mixture with non-dehydrated intermediate product **4′c**. The whole dehydration of compound **4′c** into **4c** was reached upon prolonged heating (11 h) of the reactants **1a** and **3c** under the same conditions. The non-dehydrated intermediate **4′c** can be independently prepared by refluxing reactants **1a** and **3a** in EtOH with 0.35 equiv. of H_2SO_4 as a catalyst for 5 h (see Scheme 3). Its dehydration into pyrazole **4c** was performed by heating in AcOH at 80 °C for 5 h in the presence of 1 equiv. of H_2SO_4. It is interesting to note that similar hydroxypyrazoline was not fixed in the reaction of thiazolylfuroxan **1b** with hexafluoroacetylacetone **3c**.

Since the conditions for the cyclization of thiosemicarbazide **2b** into hydrazinylthiazole **1d** are similar to those for the preparation of pyrazolylthiazoles of type **4**, it seemed reasonable to test acyclic precursor **2b** in the straightforward synthesis of such pyrazolylthiazoles **4**. To our delight, heating of reactant **2b** with dibenzoylmethane **3b** under the optimal conditions really afforded the final compound **4e** in very good yield (see Scheme 3).

Unfortunately, attempts to react some other furoxan thiazole hydrazine hydrobromides (reported in ref. 10) bearing (2-hydrazinylthiazol-4-yl) substituent at C(3) of the furoxan ring with 1,3-diketones were generally unsuccessful. Exceptionally, reaction between 4-amino-3-(2-hydrazinylthiazol-4-yl)furoxan and dibenzoylmethane **3b** under optimal conditions gave pyrazole **5** in yield of 70% (Scheme 4).

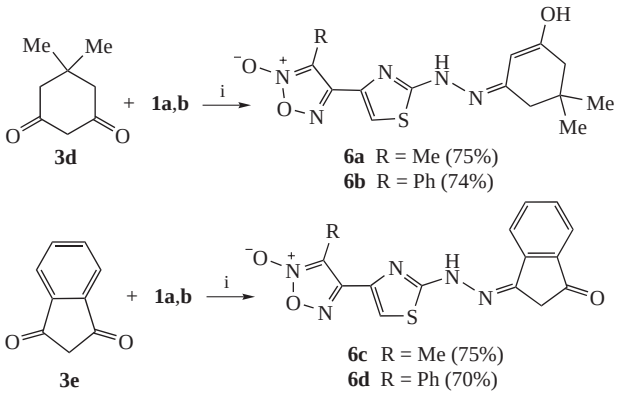


Scheme 4 *Reagents and conditions*: i, AcOH, 0.35 equiv. H_2SO_4, 80 °C, 6 h.

For further evaluation of reactivity of (thiazol-4-yl)furoxan hydrobromides **1a**,**b**, we have studied their condensation with cyclic 1,3-diketones such as dimedone **3d** and indanedione **3e** (1 : 1 molar ratio) under optimal conditions. As could be expected, the condensation proceeded only at one carbonyl group to form

† *General procedure for reaction of (2-hydrazinylthiazol-4-yl)furoxan hydrobromides* **1** *with 1,3-diketones* **3**. The suspension of compound **1** (1 mmol) in AcOH (4 ml) was stirred with 1,3-diketone **3a**–**e** (2 mmol of **3a**,**c**, or 1.4 mmol of **3b**, or 1 mmol of **3d**,**e**) in the presence of conc. H_2SO_4 (0.35 mmol) at 80 °C for 6 h. The mixture was cooled to room temperature, poured into water (10 ml), the formed precipitate was filtered, washed with water and Pr^{i}OH and dried in air. When the precipitate was not formed, AcOH was evaporated and the residue was treated similarly.

*4-[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)thiazol-4-yl]-3-methylfuroxan* **4a**. Cream solid, yield 0.26 g (93%), mp 197–198 °C, R_f 0.42 ($CHCl_3$). IR (KBr, ν/cm^{-1}): 3140, 1602, 1573, 1530, 1473, 1377, 1360, 1040, 968, 823, 775, 633. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.49 (s, 3H), 2.67 (s, 3H), 6.05 (s, 1H), 7.75 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 10.4, 14.6, 14.8, 111.4, 113.3, 117.1, 140.8, 142.5, 153.1, 153.5, 164.5. HRMS (ESI) *m*/*z*: $[M+H]^+$ 278.0720 (calc. for $C_{11}H_{12}N_5O_2S$, *m*/*z*: 278.07130).



Scheme 5 *Reagents and conditions*: i, AcOH, 0.35 equiv. H_2SO_4, 80 °C, 6 h.

hydrazones **6a**–**d** in high yields (Scheme 5). It is interesting to note that the second carbonyl group in the cyclohexane ring of compounds **6a**,**b** exists as the enol form both in solid state and in solution (an absence of C=O group absorption band in IR spectrum and a signal of C=O group in ^{13}C NMR spectra as well as an appearance of OH group signal in ^{1}H NMR spectra).

All synthesized compounds were characterized by spectral (IR and ^{1}H, ^{13}C NMR spectroscopy and HRMS) and analytical methods. The absorption bands of carbonyl group were present in IR spectra of hydrazones **6c**,**d**. In addition, resonance signals for NH groups (δ 11–12 ppm) in ^{1}H NMR spectra and for carbonyl groups (δ 199–200 ppm) in their ^{13}C NMR spectra were observed. Ultimately, the structure of compound **4f** was supported by a single-crystal X-ray diffraction study (Figure 1).‡ The DFT calculations followed by the QTAIM[17,18] and IQA[19] analysis were also performed to rationalize the molecular structure of **4f** which is the first structurally elucidated thiazolylfuroxan according to the CSD[20] search. It was found that the media affect the structure **4f** only slightly, whereas intramolecular non-covalent bonding interactions play crucial role in the conformer stabilization. The details of theoretical analysis and crystal structure determination are given in the Online Supplementary Materials.

In summary, effective synthesis of pharmacologically oriented hybrid structures [2-(1*H*-pyrazol-1-yl)thiazol-4-yl]furoxans **4a**–**f** and **5** comprising the furoxan moiety as NO-donor and pharmacophoric pyrazolylthiazole fragment has been accomplished. The synthesis is based on the formation of the pyrazole ring *via* the condensation of hydrazinyl fragment in (hydrazinylthiazol-4-yl)-furoxan hydrobromides **1** with available linear 1,3-dicarbonyl compounds **3a**–**c** in AcOH under mineral acid (HCl, H_2SO_4) catalysis. The reaction was shown to proceed through hydroxy-pyrazoline intermediate which would dehydrate into pyrazole as exemplified on hexafluoro derivative **4′c**. The condensation of (hydrazinylthiazol-4-yl)furoxans hydrobromides **1a**,**d** with cyclic 1,3-dicarbonyl compounds **3d**,**e** resulted in the monohydrazone derivatives **6a**–**d**.

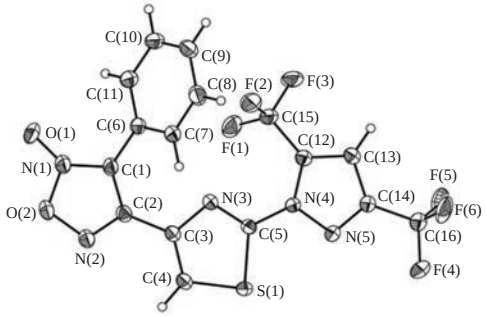


Figure 1 ORTEP view of the molecular structure of **4f** with thermal ellipsoids drawn at the 50% probability level.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.05.015.

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‡ *Crystal data for* **4f**. Colorless single crystal (0.175 × 0.123 × 0.099 mm) grown from the DMSO/acetone mixture is monoclinic, space group *C*2/*c*. At 120 K: a = 20.6989(15), b = 14.7854(11) and c = 13.9162(10) Å, β = 123.6480(10)°, V = 3545.4(4) Å^3, Z = 8, d_{calc} = 1.676 g cm^{-3}, $F(000)$ = = 1792. Intensities of 32152 reflections were measured with a Bruker APEX2 Duo CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, $2\theta < 56°$] and 4278 independent reflections (R_{int} = 0.0420) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the isotropic-anisotropic approximation. The hydrogen atoms were found in difference Fourier synthesis and refined in the isotropic approximation using riding model. The refinement converged to wR_2 = 0.1248, GOOF = 1.041 and R_1 = 0.0434 for 3403 independent reflections with $I > 2\sigma(I)$. Largest difference peak/hole: 0.747/–0.493 e Å^{-3}. All calculations were performed using SHELXL-2014/6.[21]

CCDC 1881110 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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