Unsymmetrically Substituted Furoxans. Part 19. Methyl and Phenylfuroxansulfonic Acids and Related Sulfonamides

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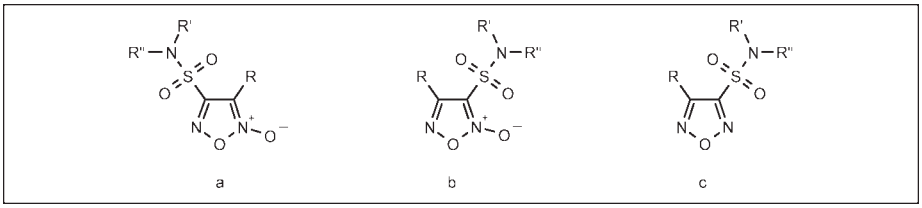

Synthesis, structural characterization, and acid dissociation constants (pK_a) of a series of methyl- and phenyl-substituted furoxansulfonic acids and related sulfonamide derivatives, as well as their furazan analogues are described. The ability of furoxans to dilate rat aorta strips precontracted with phenylephrine is reported as an example of their NO-dependent pharmacological properties.

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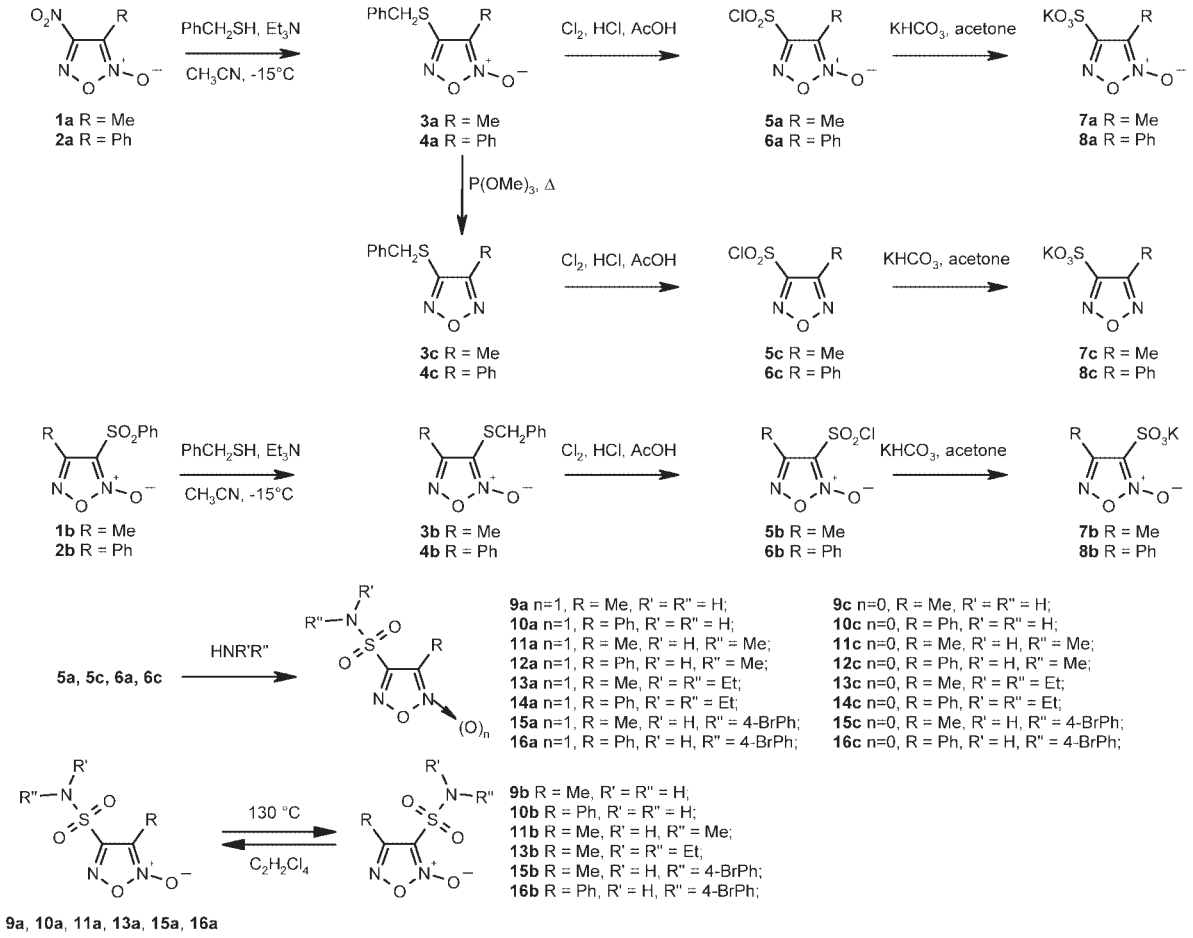
INTRODUCTION

The interest in furoxan (1,2,5-oxadiazole 2-oxide) derivatives is continuously expanding as it was shown that these products are able to release nitric oxide (NO) in physiological conditions, in the presence of thiol cofactors [1,2]. Consequently, they display a variety of pharmacological actions typical of NO [2,3]. A number of functional groups have been introduced into the simple furoxan ring, and their chemistry has been recently reviewed [4]. In previous works, we described the synthesis and chemical properties of many unsymmetrically substituted furoxans [5]. Currently we are using a number of them to design new NO-donor hybrid drugs [6,7], namely polyvalent products obtained by linking an appropriate drug, or a crucial part of it, with a NO-donor moiety through a suitable spacer. A paramount problem that must be addressed in this approach is the ''balance'' in the final hybrid of the activity deriving from its ability to release NO and the activity due to the presence of the native drug. The furoxan system seems to be a flexible NO-donor moiety for this scope as its NO-release profile can be easily modulated by changing the kind of substituent at heteroring. Surprisingly, a search in literature showed that no furoxan derivatives bearing either sulfonic or sulfonamide functions have been so far described. In this article, we report the synthesis, structural characterization, and ionization constants (pK_a) of a series of methyl- and phenyl-substituted furoxansulfonic acids and related sulfonamides, as well as their furazan analogues (1,2,5-oxadiazoles), devoid of the capacity to release NO. The ability of the furoxan derivatives to dilate rat aorta strips precontracted with phenylephrine is also discussed, as an example of their NO-dependent pharmacological properties.

RESULTS AND DISCUSSION

Chemistry. The synthesis of sulfonic acids both of the furoxan and the furazan series, and of the related sulfonamides is outlined in Scheme 1. The action of benzyl mercaptane on 4-nitro-substituted furoxans **1a**, **2a**, and 3-phenylsulfonyl-substituted furoxans **1b**, **2b** in acetonitrile solution, in the presence of triethylamine, afforded the corresponding benzylthiofuroxan derivatives **3a, 4a** and **3b, 4b**. Corresponding furazan analogues **3c, 4c** were obtained by action of refluxing trimethyl phosphite on **3a** and **4a**, respectively. All these sulphur intermediates were transformed in the related sulfonyl chlorides **5a-c**, **6a-c** by action of chlorine in acetic acid solution in presence of hydrochloric acid. In this reaction, benzyl chloride formed in equimolar amount with the expected sulfonyl chlorides. Solid sulfonyl chlorides **6a** and **6c** were purified by crystallization. All the attempts to isolate **5a-c** and **6b** failed due to their thermal and hydrolytic instability. Consequently, these compounds were used for further reactions in mixture with benzyl chloride. All sulfonyl chlorides afforded the final sulfonic acid potassium salts **7a-c**, **8a-c**, when treated with 1*N* $KHCO_3$ in acetone solution. Sulfonamides derivatives of 3-phenyl and 3-methylfuroxan series **9a**-**16a** and related furazans **9c**-**16c** were obtained by action of the appropriate amines on the

Scheme 1



corresponding sulfonyl chlorides in CH_2Cl_2, or in water solution when ammonia or methylamine were used. This synthetic approach failed in the preparation of the sulfonamide isomers of the 4-phenyl and 4-methylfuroxans series owing to the decomposition of the related sulfonyl chlorides in the presence of amine reagents. Consequently, we obtained the sulfonamides **9b**, **10b**, **11b**, **13b**, **15b**, and **16b** by thermal isomerization of the corresponding 3-phenyl and 3-methyl isomers at 130°C in 1,1,2,2-tetrachloroethane ($Cl_2CHCHCl_2$) solution. After solvent removal the mixtures of isomers were separated by HPLC. This separation failed in the case of **12a/12b** and **14a/14b** mixtures. The equilibrium constants (NMR or HPLC detection) between the isomer pair of sulfonamides, determined at 130°C in $Cl_2CHCHCl_2$, are listed in Table 1. In some cases the equilibrium was approached from both sides. In all cases the isomers bearing the sulfonamido groups from the opposite side of the exocyclic oxygen are favoured. ^1H and ^{13}C NMR spectra (Experimental) are in keeping with the structural assignments. In particular, in the case of the furoxan isomers they satisfy the rule that both in ^1H and in ^{13}C NMR spectra, the 3-CH_3 resonance signal is upfield with respect to the one of 4-CH_3 [8,9] and that in the ^{13}C NMR spectra the resonances of C(1) and C(4) carbons of the 3-Ph group appear upfield with respect to the corresponding resonances of the 4-Ph group [10]. Finally the chemical shift of C3 and C4 carbon atoms of the furoxan ring are in keeping with those observed in aryl- and alkylsulfonyl furoxans [9,11].

Ionization constants. The pK_a values of sulfonamide derivatives both of the furoxan and of the furazan series were measured by potentiometric technique using a Sirius GLpK_a apparatus. These values are listed in Table 1. The high acid strength of all the sulfonic acids, which are in keeping with the electron withdrawing properties of the furazan and furoxan rings [12], did not allow the detection of their dissociation constants with this technique. Some interesting structural considerations can be derived from the analysis of Table 1. In a pair of isomers the product bearing the sulfonamide function at the 4-position is always just a little less acid than the other isomer or displays the same acidity. The related furazans are always less acidic than the related furoxans. In

Table 1

Physicochemical parameters and pharmacological activities of furoxan and furazan sulfonic acids (**7, 8**) and related sulfonamides (**9–16**).

Comp.	Molecular formula	mp (crystallization solvent)	pK_a ± SD	Thermal isomerization equilibrium K ([a]/[b])	Vasodilator activity	
					EC_{50} ± SE (μ*M*)	EC_{50} ± SE (μ*M*) + 1 μ*M* ODQ
7a	$C_3H_3KN_2O_5S$	>280°C dec. (H_2O)	ND		ND[d]	ND[d]
7b	$C_3H_3KN_2O_5S$	277–279°C dec. (H_2O)	ND		24 ± 6	ND[d]
7c	$C_3H_3KN_2O_4S$	>270°C dec. without melting (H_2O)	ND		–	–
8a	$C_8H_5KN_2O_5S$	214–215°C dec. (H_2O)	ND		37 ± 4	ND[d]
8b	$C_8H_5KN_2O_5S$	250–255°C dec. (H_2O)	ND		4.3 ± 0.8	ND[d]
8c	$C_8H_5KN_2O_4S \cdot {}^3/_4H_2O$	255–260°C dec. (H_2O)	ND		–	–
9a	$C_3H_5N_3O_4S$	93–93.5°C ($ClCH_2CH_2Cl$)	6.85 ± 0.01	2.05[b]	ND[d]	ND[d]
9b	$C_3H_5N_3O_4S$	117–118°C ($ClCH_2CH_2Cl$)	6.80 ± 0.01		27 ± 3	ND[d]
9c	$C_3H_5N_3O_3S$	81–82°C ($ClCH_2CH_2Cl/CCl_4$)	7.06 ± 0.02		–	–
10a	$C_8H_7N_3O_4S \cdot {}^1/_2H_2O$	147–148°C (H_2O)	6.88 ± 0.01	1.94[c]	1.4 ± 0.2	ND[d]
10b	$C_8H_7N_3O_4S$	112–114°C (H_2O)	6.76 ± 0.01		0.61 ± 0.11	96 ± 16
10c	$C_8H_7N_3O_3S$	149.5–151°C (H_2O)	7.16 ± 0.01		–	–
11a	$C_4H_7N_3O_4S$	77–78°C (CCl_4)	8.03 ± 0.01	2.11[b]	21 ± 3	ND[d]
11b	$C_4H_7N_3O_4S$	48–50°C (CCl_4)	8.10 ± 0.01		2.4 ± 0.3	ND[d]
11c	$C_4H_7N_3O_3S$	55–55.5°C (CCl_4)	8.43 ± 0.01		–	–
12a	$C_9H_9N_3O_4S$	108–109°C (H_2O)	8.12 ± 0.01[a]		0.15 ± 0.02	10 ± 1
12c	$C_9H_9N_3O_3S$	94–95°C (H_2O)	8.58 ± 0.01[a]		–	–
13a	$C_7H_{13}N_3O_4S$	54–55°C (hexane)	–	3.30[b]	7.3 ± 0.7	ND[d]
13b	$C_7H_{13}N_3O_4S$	92–93°C (hexane)	–		0.087 ± 0.011	11 ± 3
13c	$C_7H_{13}N_3O_3S$	liquid	–		–	–
14a	$C_{12}H_{15}N_3O_4S$	64–65°C (hexane)	–		0.070 ± 0.014	6.5 ±1.1
14c	$C_{12}H_{15}N_3O_3S$	liquid	–		–	–
15a	$C_9H_8BrN_3O_4S \cdot {}^1/_2H_2O$	126–127°C (CCl_4)	4.56 ± 0.01[a]	1.52[b]	[e]	[e]
15b	$C_9H_8BrN_3O_4S$	114.5–115.5°C (CCl_4)	4.43 ± 0.01[a]		[e]	[e]
15c	$C_9H_8BrN_3O_3S$	96.5–97.5°C (CCl_4)	5.15 ± 0.01[a]		[e]	[e]
16a	$C_{14}H_{10}BrN_3O_4S$	149–150°C (CCl_4)	4.72 ± 0.01[a]	2.15[c]	[e]	[e]
16b	$C_{14}H_{10}BrN_3O_4S$	158–159°C (CCl_4)	4.51 ± 0.01[a]		[e]	[e]
16c	$C_{14}H_{10}BrN_3O_3S$	131–132°C (CCl_4)	5.20 ± 0.2[a]		[e]	[e]

[a] Potentiometric titrations were performed in water containing methanol as a cosolvent in different ratios depending on the solubility of compounds: pK_a values were determined by extrapolation at 0% methanol using the Yasuda-Shedlovsky procedure (experimental).
[b] NMR determination.
[c] HPLC determination.
[d] EC_{50} could not be calculated as the relaxation at maximum concentration tested (100 μ*M*) did not reach 50%.
[e] The product completely relaxed the contracted tissue in a concentration independent manner; the tissue did not recover its contractility.

all the series, the presence on sulfonamide function of the *p*-bromophenyl group increases the acidity while the presence of the methyl group decreases it. This is in accordance with the ability of the former to delocalize the negative charge of the conjugated anion and with the opposite effect exerted by the latter.

Vasodilator activity. Furoxan derivatives display vasodilator properties. It is commonly accepted that this is due to their ability to release NO under the action of vessel intracellular thiols. The NO produced activates soluble guanylate cyclase (sGC) and this induces a series of events whose final result is dilation of the vessel [13]. All furoxansulfonamides described in this work were able to relax rat aorta strips precontracted with phenylephrine in a concentration dependent manner. The vasodilator potencies EC_{50}, namely the molar concentration able to induce 50% of the relaxing effect to the contracted tissue are reported in Table 1. When the experiments were repeated in the presence of 1 μ*M* 1*H*-[1,2,4]oxadiazolo[4,3-a]quinoxalin-1-one (ODQ), a decrease in the potencies was observed, in keeping with a NO-induced activation of the sGC as the mechanism, which underlies this effect. Products bearing a *p*-bromophenyl moiety behaved differently. They completely relaxed the contracted tissue in a concentration independent manner, both in the presence and in the absence of ODQ. In addition, the tissue did not recover its contractility in spite of extensive washing. It is worthy of note that also the furazan analogues **15c** and **16c** display similar behavior. This indicates that the vasodilator activity of these specific products is not NO dependent but probably connected with their tissue toxicity.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 at 300 and 75 MHz, respectively, using $SiMe_4$ as

the internal standard. Low resolution mass spectra were recorded with a Finnigan-Mat TSQ-700. Melting points were determined with a capillary apparatus (Buchi 540). Flash column chromatography was performed on silica gel (Merck Kieselgel 60, 230–400 mesh ASTM), using the indicated eluents; PE stands for 40–60 petroleum ether. The progress of the reactions was followed by thin layer chromatography (TLC) on 5 × 20 cm plates with a layer thickness of 0.2 mm. Anhydrous magnesium sulfate was used as the drying agent for the organic phases. Organic solvents were removed under vacuum at 30°C. Preparative HPLC was performed on a LiChrospher® C18 column (250 × 25 mm, 10 μm) (Merck Darmstadt, Germany) with a Varian ProStar mod-210 with Varian UV detector mod-325. Elemental analyses (C, H, N) were performed by REDOX (Monza). Compounds **1a** [14], **2a** [15], **1b** [9], and **2b** [16] were synthesized as described elsewhere.

General procedure for preparation of benzylthiofuroxans (3a,b and 4a,b). To a stirred solution of appropriate furoxan derivative (24 mmol) in CH_3CN (25 mL), cooled at −15°C, Et_3N (3.4 mL, 24 mmol) was added. To the obtained solution benzylmercaptane (2.5 mL, 24 mmol) was added in one portion and the reaction was stirred at −15°C for 30 min. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature for an additional 30 min. Benzylthiofuroxans were isolated as described.

4-Benzylthio-3-methylfuroxan (3a). The reaction mixture was diluted with CH_2Cl_2. The organic solvent was washed with H_2O, 1*N* HCl, $NaHCO_3$ saturated solution, brine, dried, and evaporated. The obtained oil was solidified by treating with PE at 0°C. The obtained solid was filtered, washed with cold PE, and crystallized from hexane to give the title compound as a white solid, yield 54%, mp 48–49°C (hexane); ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3), 4.38 (s, 2H, CH_2), 7.31–7.38 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 7.5 (3-*C*H_3), 35.2, 112.5 (*C*3 fx), 128.1, 128.8, 129.1, 135.4, 154.8 (*C*4 fx); ms: *m*/*z* 222 (M^+). *Anal*. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.35; H, 4.51; N, 12.73.

3-Benzylthio-4-methylfuroxan (3b). The reaction mixture was diluted with CH_2Cl_2. The organic solvent was washed with H_2O, 1*N* HCl, $NaHCO_3$ saturated solution, brine, dried, and evaporated. The obtained oil was purified by flash chromatography (eluent 8/2 PE/CH_2Cl_2) to give the title compound as a colorless oil, yield 79%; ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 7.14–7.18 (m, 2H) 7.24–7.31 (m, 3H) (C_6H_5); ^{13}C NMR ($CDCl_3$): δ 10.9 (4-*C*H_3), 34.9, 111.2 (*C*3 fx), 128.0, 128.7, 128.9, 135.4, 157.1 (*C*4 fx); ms: *m*/*z* 222 $(M)^+$. *Anal*. Calcd. for $C_{10}H_{10}N_2O_2S$: C, 54.04; H, 4.53; N, 12.60. Found: C, 54.26; H, 4.46; N, 12.42.

4-Benzylthio-3-phenylfuroxan (4a). The product precipitated from the reaction mixture. It was filtered, washed with cold CH_3CN, and crystallized from EtOH to give the title compound as a white solid, yield 57%, mp 111–113°C (EtOH); ^{1}H NMR ($CDCl_3$): δ 4.45 (s, 2H, CH_2), 7.31–7.49 (m, 8H), 7.83–7.87 (m, 2H) (2C_6H_5); ^{13}C NMR ($CDCl_3$): δ 35.5, 114.1 (*C*3 fx), 122.4 (*C*1 Ph), 127.3, 128.1, 128.8, 129.0, 129.3, 130.7 (*C*4 Ph), 135.0, 154.1 (*C*4 fx); ms: *m*/*z* 284 $(M)^+$. *Anal*. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.58; H, 4.23; N, 9.84.

3-Benzylthio-4-phenylfuroxan (4b). The organic solvent was removed and the obtained oil was purified by flash chromatography (eluent 7/3 PE/CH_2Cl_2) to give the title compound as a colorless oil, yield 85%; ^{1}H NMR (DMSO-d_6): δ 4.16 (s, 2H, CH_2), 7.07–7.25 (m, 5H) 7.39–7.51 (m, 3H), 7.59–7.61 (m, 2H) (2C_6H_5); ^{13}C NMR ($CDCl_3$): δ 34.7, 110.6 (*C*3 fx), 126.1 (*C*1 Ph), 127.7, 128.0, 128.7, 128.8, 131.0, 135.5, 157.7 (*C*4 fx); ms: *m*/*z* 284 $(M)^+$. *Anal*. Calcd. for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.15; H, 4.28; N, 9.87.

General procedure for preparation of benzylthiofurazans (3c and 4c). A solution of appropriate furoxan (45 mmol) in $P(OMe)_3$ (30 mL, 0.25 mol) was heated at reflux for 12 h. The reaction was cooled and poured into an ice/4*N* HCl (80 mL) mixture. The precipitate formed was filtered, washed with cold water and crystallized from MeOH to give the title compound as a white crystalline solid.

3-Benzylthio-4-methylfurazan (3c). Yield: 77%, mp 28–28.5°C (MeOH); ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 7.25–7.41 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$): δ 8.0, 36.8, 128.0, 128.8, 129.1, 135.7, 149.8, 152.2; ms: *m*/*z* 206 (M^+). *Anal*. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.23; H, 4.89; N, 13.58. Found: C, 58.20; H, 5.00; N, 13.60.

3-Benzylthio-4-phenylfurazan (4c). Yield 81%, mp 65.5–66.5°C (MeOH); ^{1}H NMR ($CDCl_3$): δ 4.49 (s, 2H, CH_2), 7.25–7.49 (m, 8H), 7.80–7.82 (m, 2H) (2C_6H_5); ^{13}C NMR ($CDCl_3$): δ 37.3, 125.3, 128.0, 128.0, 128.8, 129.0, 129.2, 130.7, 135.4, 151.1, 152.3; ms: *m*/*z* 268 (M^+). *Anal*. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.24; H, 4.49; N, 10.45.

General procedure for preparation of sulfonylchlorides (5a-c and 6a-c). To the suspension/solution of benzylthioderivatives in acetic acid 4*N* HCl (0.5 mL) was added and chlorine was bubbled through reaction mixture for 2 h. After this time reaction, the mixture was stirred at room temperature for 1 h, then it was poured into H_2O and extracted with PE. The organic phase was washed with H_2O (3×), brine, dried, and evaporated. The obtained products were crystallized from hexane (in case of solids **6a** and **6c**) or used directly for further reaction in mixture with benzylchloride (1/1 molar ratio).

3-Phenylfuroxan-4-sulfonyl chloride (6a). White solid, yield 80%, mp 94–96°C (hexane); ^{1}H NMR ($CDCl_3$): δ 7.56–7.61 (m, 3H), 7.75–7.79 (m, 2H) (C_6H_5); ^{13}C NMR ($CDCl_3$) δ: 110.8 (*C*3 fx), 119.3 (*C*1 Ph), 129.1, 129.4, 132.1 (*C*4 Ph), 158.2 (*C*4 fx); ms: *m*/*z* 260/262 (M^+). *Anal*. Calcd. for $C_8H_5ClN_2O_4S$: C, 36.86; H, 1.93; N, 10.75. Found: C, 37.05; H, 1.99; N, 10.75.

3-Phenylfurazan-4-sulfonyl chloride (6c). White solid, yield 58%, mp 52–53°C (hexane); ^{1}H NMR ($CDCl_3$): δ 7.54–7.67 (m, 3H), 7.76–7.82 (m, 2H) (C_6H_5); ^{13}C NMR ($CDCl_3$) δ: 122.0, 129.3, 129.4, 132.2, 151.5, 156.9; ms: *m*/*z* 244/246 (M^+). *Anal*. Calcd. for $C_8H_5ClN_2O_3S$: C, 39.27; H, 2.06; N, 11.45. Found: C, 39.34; H, 2.21; N, 11.30.

General procedure for preparation of sulfonic acid potassium salts (7a-c and 8a-c). To a solution of the appropriate sulfonylchloride (2.5 mmol) in acetone (20 mL) 1*N* $KHCO_3$ (7.5 mL, 7.5 mmol) was added at 0°C. The reaction was allowed to reach room temperature and stirred for 2 h. The organic solvent was evaporated, the residue was dissolved in H_2O and the resulting solution was washed with CH_2Cl_2 (2×), filtered, and evaporated. The obtained solid was crystallized from water to give the title compound as a white solid.

Potassium 3-methylfuroxan-4-sulfonate (7a). White solid, yield 38% (for two synthetic steps), mp > 280°C dec. (H_2O); ^{1}H NMR (D_2O): δ 2.31 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 7.7 (3-*C*H_3), 114.9 (*C*3 fx), 160.5 (*C*4 fx). *Anal*. Calcd. for $C_3H_3KN_2O_5S$: C, 16.51; H, 1.39; N, 12.83. Found: C, 16.46; H, 1.41; N, 12.76.

Potassium 4-methylfuroxan-3-sulfonate (7b). White solid, yield 15% (for two synthetic steps), mp 277–280°C dec. (H_2O); ^{1}H NMR (D_2O): δ 2.47 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 12.1 (4-*C*H_3), 120.2 (*C*3 fx), 154.4 (*C*4 fx). *Anal*. Calcd. for $C_3H_3KN_2O_5S$: C, 16.51; H, 1.39; N, 12.83. Found: C, 16.45; H, 1.50; N, 12.65.

Potassium 3-methylfurazan-4-sulfonate (7c). White solid, yield 34% (for two synthetic steps), mp > 270°C dec. without melting (H_2O); ^{1}H NMR (D_2O): δ 2.06 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 8.4, 150.8, 157.5. *Anal*. Calcd. for $C_3H_3KN_2O_4S$: C, 17.82; H, 1.50; N, 13.85. Found: C, 17.71; H, 1.52; N, 13.66.

Potassium 3-phenylfuroxan-4-sulfonate (8a). White solid, yield 45%, mp 214–215°C (H_2O); ^{1}H NMR (D_2O): δ 7.58–7.60 (m, 3H), 7.86–7.90 (m, 2H) (C_6H_5); ^{13}C NMR (D_2O): δ 116.0 (*C*3 fx), 121.7 (*C*1 Ph), 129.4, 129.6, 132.0 (*C*4 Ph), 159.7 (*C*4 fx). *Anal*. Calcd. for $C_8H_5KN_2O_5S$: C, 34.28; H, 1.80; N, 9.99. Found: C, 34.05; H, 1.79; N, 9.83.

Potassium 4-phenylfuroxan-3-sulfonate (8b). White solid, yield 35% (for two synthetic steps), mp 250–255°C (H_2O); ^{1}H NMR (D_2O): δ 7.55–7.65 (m, 3H), 7.76–7.79 (m, 2H) (C_6H_5); ^{13}C NMR (D_2O): δ 119.4 (*C*3 fx), 126.1 (*C*1 Ph), 129.3, 129.7, 132.1 (*C*4 Ph), 156.4 (*C*4 fx). *Anal*. Calcd. for $C_8H_5KN_2O_5S$: C, 34.28; H, 1.80; N, 9.99. Found: C, 34.28; H, 1.93; N, 9.97.

Potassium 3-phenylfurazan-4-sulfonate (8c). White solid, yield 75%, mp 255–260°C (H_2O); ^{1}H NMR (D_2O): δ 7.55–7.64 (m, 3H), 7.92–7.95 (m, 2H) (C_6H_5); ^{13}C NMR (D_2O): δ 124.4, 129.6, 129.7, 132.0, 153.1, 156.6. *Anal*. Calcd. for $C_8H_5KN_2O_4S$ $^3/_4H_2O$: C, 34.58; H, 2.35; N, 10.08. Found: C, 34.50; H, 2.17; N, 10.07.

General procedure for preparation of sulfonylamides (9a, 9c, 10a, and 10c) and *N*-methyl sulfonylamides (11a, 11c, 12a, and 12c). An appropriate sulfonylchloride derivative was added to the vigorously stirred concentrated solution of amine in H_2O at −10°C. The ice-salt bath was removed and the reaction was stirred for 2 h at room temperature. Then reaction mixture was cooled again, the pH was adjusted to one with concentrated HCl and the product was purified as described.

3-Methylfuroxan-4-sulfonamide (9a). The acidified mixture was extracted with EtOAc. The organic phase was washed with H_2O, brine, dried, and evaporated. The resulting oil was purified by flash chromatography (eluent 8/2 PE/EtOAc) to give the colorless oil, which solidified at −78°C. The title compound was crystallized from 1,2-dichloroethane. White solid, yield 50% (for two synthetic steps), mp 93–93.5°C (1,2-dichloroethane); ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 8.67 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 7.7 (3-*C*H_3), 110.9 (*C*3 fx), 160.2 (*C*4 fx); ms: *m*/*z* 179 (M^+). *Anal*. Calcd. for $C_3H_5N_3O_4S$: C, 20.11; H, 2.81; N, 23.45. Found: C, 20.07; H, 2.86; N, 23.34.

3-Methylfurazan-4-sulfonamide (9c). The acidified mixture was extracted with EtOAc. The organic phase was washed with H_2O, brine, dried, and evaporated. The resulting oil was purified by flash chromatography (eluent 8/2 PE/EtOAc) to give the colorless oil, which solidified at −78°C. The title compound was crystallized from 1,2-dichloroethane/CCl_4 mixture. White solid, yield 34% (for two synthetic steps), mp 81–82°C (1,2-dichloroethane/CCl_4); ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 8.66 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 8.1, 149.6, 157.8; ms: *m*/*z* 164 [(M+H)$^+$]. *Anal*. Calcd. for $C_3H_5N_3O_3S$: C, 22.08; H, 3.09; N, 25.75. Found: C, 22.10; H, 3.08; N, 25.50.

3-Phenylfuroxan-4-sulfonamide (10a). Product precipitated from acidified reaction mixture. It was filtered, washed with cold H_2O, and crystallized from H_2O to give the title compound as a white solid, yield 75%, mp 147–148°C (H_2O); ^{1}H NMR (DMSO-d_6): δ 7.57–7.64 (m, 3H), 7.85–7.90 (m, 2H) (C_6H_5), 8.81 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 112.7 (*C*3 fx), 121.0 (*C*1 Ph), 128.7, 128.8, 131.0 (*C*4 Ph), 159.7 (*C*4 fx); ms: *m*/*z* 242 [(M+H)$^+$]. *Anal*. Calcd. for $C_8H_7N_3O_4S$ $^1/_2H_2O$: C, 38.40; H, 3.22; N, 16.79. Found: C, 38.45; H, 3.34; N, 16.42.

3-Phenylfurazan-4-sulfonamide (10c). The product precipitated from acidified reaction mixture. It was filtered, washed with cool water, and crystallized from H_2O to give the title compound as a white solid, yield 72%, mp 149.5–151°C (H_2O); ^{1}H NMR (DMSO-d_6): δ 7.57–7.68 (m, 3H), 7.89–7.97 (m, 2H) (C_6H_5), 8.92 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 123.3, 129.1 (two signals overlapped), 131.5, 151.9, 157.3; ms: *m*/*z* 225 [(M+H)$^+$]. *Anal*. Calcd. for $C_8H_7N_3O_3S$: C, 42.66; H, 3.13; N, 18.65. Found: C, 42.62; H, 3.19; N, 18.54.

***N*-Methyl-3-methylfuroxan-4-sulfonamide (11a).** The acidified reaction mixture was extracted with CH_2Cl_2. The organic solvent was washed with H_2O, brine, dried, and evaporated. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, yield 61% (for two synthetic steps), mp 77–79°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 2.13 (s, 3H, CH_3), 3.01 (d, 3H, CH_3), 5.19 (broad s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 8.0 (3-*C*H_3), 30.2, 110.3 (*C*3 fx), 157.9 (*C*4 fx); ms: *m*/*z* 193 (M^+). *Anal*. Calcd. for $C_4H_7N_3O_4S$: C, 24.87; H, 3.65; N, 21.75. Found: C, 24.79; H, 3.77; N, 21.41.

***N*-Methyl-3-methylfurazan-4-sulfonamide (11c).** The acidified reaction mixture was extracted with EtOAc. The organic solvent was washed with H_2O, brine, dried, and evaporated. The obtained oil was purified by flash chromatography (eluent 9/1 PE/EtOAc) to give the colorless oil, which solidified by treating with PE at −78°C. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, yield 32% (for two reaction steps), mp 55–55.5°C (CCl_4); ^{1}H NMR (DMSO-d_6): δ 2.53 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 8.79 (br.s., 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ 8.2, 28.6, 149.9, 155.2; ms: *m*/*z* 178 [(M+H)$^+$]. *Anal*. Calcd. for $C_4H_7N_3O_3S$: C, 27.12; H, 3.98; N, 23.72. Found: C, 27.11; H, 4.01; N, 23.60.

***N*-Methyl-3-phenylfuroxan-4-sulfonamide (12a).** The acidified reaction mixture was kept at 4°C overnight. The next day a precipitate formed, was filtered, washed with cold H_2O, and crystallized from H_2O to give the title compound as a white solid, yield 77%, mp 108–109°C (H_2O); ^{1}H NMR ($CDCl_3$): δ 3.02 (d, 3H, CH_3), 5.04–5.13 (m, 1H, N*H*), 7.54–7.56 (m, 3H), 7.93–7.96 (m, 2H) (C_6H_5); ^{13}C NMR ($CDCl_3$): δ 30.7, 112.5 (*C*3 fx), 120.6 (*C*1 Ph), 128.5, 129.1, 131.5 (*C*4 Ph), 157.4 (*C*4 fx); ms: *m*/*z* 255 (M^+). *Anal*. Calcd. for $C_9H_9N_3O_4S$: C, 42.35; H, 3.55; N, 16.46. Found: C, 42.31; H, 3.57; N, 16.43.

***N*-Methyl-3-phenylfurazan-4-sulfonamide (12c).** The product precipitated from acidified reaction mixture was filtered, washed with cold H_2O, and crystallized from H_2O to give the title compound as a white solid, yield 84%, mp 94–95°C (H_2O); ^{1}H NMR (DMSO-d_6): δ 2.79 (s, 3H, CH_3), 7.59–7.68 (m, 3H), 7.91–7.94 (m, 2H) (C_6H_5), 9.11 (s, 2H, NH_2); ^{13}C NMR (DMSO-d_6): δ 29.1, 123.2, 129.0, 129.1, 131.5, 152.2,

155.0; ms: *m*/*z* 239 (M^+). *Anal*. Calcd. for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.56. Found: C, 45.27; H, 3.66; N, 17.52.

General procedure for preparation *N*,*N*-diethylsulfonamides (13a, 13c 14a, and 14c). To the solution of corresponding sulfonylchloride (1.9 mmol) in CH_2Cl_2 (15 mL) a solution of Et_2NH (0.50 mL, 4.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0°C. The ice bath was removed and the reaction was stirred at room temperature for 1 h. The obtained solution was washed with 1*N* HCl, H_2O, $NaHCO_3$ saturated solution, brine, dried, and evaporated. The obtained oil was purified by flash chromatography with the indicated eluents.

***N*,*N*-Diethyl-3-methylfuroxan-4-sulfonamide (13a).** The obtained oil was purified by flash chromatography (eluent 7/3 PE/CH_2Cl_2) to give a solid, which was crystallized from hexane to give the title compound as a white solid, yield 36% (for two reaction steps), mp 54–55°C (hexane); ^{1}H NMR ($CDCl_3$): δ 1.30 (t, 6H, 2C*H*$_3$), 2.35 (s, 3H, C*H*$_3$), 3.49 (q, 4H, 2C*H*$_2$); ^{13}C NMR ($CDCl_3$): δ 8.1 (3-*C*H$_3$), 14.4, 43.4, 110.4 (*C*3 fx), 158.7 (*C*4 fx); ms: *m*/*z* 235 (M^+). *Anal*. Calcd. for $C_7H_{13}N_3O_4S$: C, 35.74; H, 5.57; N, 17.86. Found: C, 35.97; H, 5.59; N, 17.69.

***N*,*N*-Diethyl-3-methylfurazan-4-sulfonamide (13c).** The obtained oil was purified by flash chromatography (eluent 8/2 PE/CH_2Cl_2) to give the title compound as colorless oil, yield 35% (for two reaction steps); ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 6H, 2C*H*$_3$), 2.54 (s, 3H, C*H*$_3$), 3.39 (q, 4H, 2C*H*$_2$); ^{13}C NMR ($CDCl_3$): δ 8.4, 14.2, 42.8, 150.6, 156.5; ms: *m*/*z* 219 (M^+). *Anal*. Calcd. for $C_7H_{13}N_3O_3S$: C, 38.35; H, 5.98; N, 19.16. Found: C, 38.40; H, 5.99; N, 19.06.

***N*,*N*-Diethyl-3-phenylfuroxan-4-sulfonamide (14a).** The obtained oil was purified by flash chromatography (eluent 7/3 PE/CH_2Cl_2) to give a pale yellow oil, which became solid on standing. The title product was obtained by crystallization from hexane, yield 57%, mp 64–65°C (hexane); ^{1}H NMR (CDCl3): δ 1.28 (t, 6H, 2C*H*$_3$), 3.48 (q, 4H, 2C*H*$_2$), 7.50–7.54 (m, 3H), 7.94–7.97 (m, 2H) (C$_6$*H*$_5$); ^{13}C NMR ($CDCl_3$): δ 14.7, 44.0, 112.7 (*C*3 fx), 120.9 (*C*1 Ph), 128.6, 129.0, 131.3 (*C*4 Ph), 157.9 (*C*4 fx);. ms: *m*/*z* 298 [$(M+H)^+$]. *Anal*. Calcd. for $C_{12}H_{15}N_3O_4S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.30; H, 5.00; N, 13.92.

***N*,*N*-Diethyl-3-phenylfurazan-4-sulfonamide (14c).** The obtained oil was purified by flash chromatography (eluent 9/1 PE/CH_2Cl_2) to give the pale yellow oil, which was further purified with HPLC (75/25 CH_3CN/H_2O) to give the title compound as a colorless oil, yield 84%; ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 6H, 2C*H*$_3$), 3.49 (q, 4H, 2C*H*$_2$), 7.49–7.59 (m, 3H), 7.98–8.00 (m, 2H) (C$_6$*H*$_5$); ^{13}C NMR ($CDCl_3$): δ 14.3, 43.3, 123.1, 129.0, 129.1, 131.5, 152.3, 154;. ms: *m*/*z* 281 (M^+). *Anal*. Calcd. for $C_{12}H_{15}N_3O_3S$: C, 51.23; H, 5.37; N, 14.93. Found: C, 50.91; H, 5.42; N, 15.10.

General procedure for preparation *N*-(4-bromophenyl)-sulfonamides (15a, 15c 16a, and 16c). To a solution of the appropriate sulfonylchloride (1.2 mmol) in CH_2Cl_2 (15 mL) *p*-bromoaniline (0.50 g, 2.9 mmol) was added and the reaction was stirred at room temperature for 4 days. The obtained solution was diluted with CH_2Cl_2 washed with 1*N* HCl, H_2O, brine, dried, and evaporated. The obtained solids were crystallized from CCl_4 to give the title compounds as white solids.

***N*-(4-Bromophenyl)-3-methylfuroxan-4-sulfonamide (15a).** Yield 50% (for two reaction steps), mp 126–127°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 2.20 (s, 3H, C*H*$_3$), 7.17–7.22 (m, 3H), 7.48–7.53 (m, 2H), (C$_6$*H*$_4$ + N*H*); ^{13}C NMR ($CDCl_3$): δ 8.0 (3-*C*H$_3$), 110.3 (*C*3 fx), 121.4, 125.7, 132.9, 132.9, 157.4 (*C*4 fx); ms: *m*/*z* 333/335 (M^+). *Anal*. Calcd. for $C_9H_8BrN_3O_4S$ ½H_2O: C, 31.50; H, 2.64; N, 12.25. Found: C, 31.25; H, 2.34; N, 11.86.

***N*-(4-Bromophenyl)-3-methylfurazan-4-sulfonamide (15c).** Yield 42% (for two reaction steps), mp 96.5–97.5°C (CCl_4); ^{1}H NMR (DMSO-d_6): δ 2.48 (s, 3H, C*H*$_3$), 7.14–7.19 (m, 2H), 7.55–7.60 (m, 2H), (C$_6$*H*$_4$), 11.69 (broad s., 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ 8.1, 118.1, 123.5, 132.3, 134.9, 150.0, 155.1; ms: *m*/*z* 317/319 (M^+). *Anal*. Calcd. for $C_9H_8BrN_3O_3S$: C, 33.98; H, 2.53; N, 13.20. Found: C, 33.93; H, 2.44; N, 13.14.

***N*-(4-Bromophenyl)-3-phenylfuroxan-4-sulfonamide (16a).** Yield 76%, mp 149–150°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 7.03 (s, 1H, N*H*), 7.11 (d, 2H), 7.43 (d, 2H) (C$_6$*H*$_4$), 7.53–7.54 (m, 3H), 7.79–7.82 (m, 2H) (C$_6$*H*$_5$); ^{13}C NMR ($CDCl_3$): δ 112.3 (*C*3 fx), 120.1, 121.0 (*C*1 Ph), 125.3, 128.6, 129.2, 131.5 (*C*4 Ph), 132.7, 133.1, 156.8 (*C*4 fx); ms: *m*/*z* 395/397 (M^+). *Anal*. Calcd. for $C_{14}H_{10}BrN_3O_4S$: C, 42.44; H, 2.54; N, 10.61. Found: C, 42.15; H, 2.55; N, 10.45.

***N*-(4-Bromophenyl)-3-phenylfurazan-4-sulfonamide (16c).** Yield 79%, mp 131–132°C (CCl_4); ^{1}H NMR (DMSO-d_6): δ 7.19 (d, 2H), 7.48 7.71 (m, 5H), 7.78–7.87 (m, 2H) (C$_6$*H*$_5$ + C$_6$*H*$_4$), 11.94 (broad s. 1H, N*H*); ^{13}C NMR (DMSO-d_6): δ 118.0, 122.8, 123.5, 129.0, 129.2, 131.5, 132.2, 135.2, 152.3, 154.9; ms: *m*/*z* 379/381 (M^+). *Anal*. Calcd. for $C_{14}H_{10}BrN_3O_3S$: C, 44.23; H, 2.65; N, 11.05. Found: C, 44.10; H, 2.64; N, 11.03.

General procedure for thermal isomerization of furoxansulfonamides (9b, 10b, 13b, 15b, 16b). A solution of the appropriate 3-methyl or 3-phenyl sulfonamide derivative in $Cl_2CHCHCl_2$ was heated at 130°C for 24 h. The solvent was evaporated and the obtained mixture of isomers was separated by HPLC with the eluent indicated. Analytically pure samples of 4-methyl and 4-phenyl substituted furoxansulfonamides were obtained by crystallization.

4-Methylfuroxan-3-sulfonamide (9b). HPLC (70/30 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min), second eluted. The obtained solid was crystallized from 1,2-dichloroethane to give the title compound as a white crystalline solid, mp 117–118°C (1,2-dichloroethane); ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, C*H*$_3$), 8.29 (s, 2H, N*H*$_2$); ^{13}C NMR (DMSO-d_6): δ 12.5 (4-*C*H$_3$), 119.1 (*C*3 fx), 153.2 (*C*4 fx); ms: *m*/*z* 179 (M^+). *Anal*. Calcd. for $C_3H_5N_3O_4S$: C, 20.11; H, 2.81; N, 23.45. Found: C, 20.19; H, 2.70; N, 23.41.

4-Phenylfuroxan-3-sulfonamide (10b). HPLC (40/60 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min), second eluted. The obtained solid was crystallized from H_2O to give the title compound as a white crystalline solid, mp 112–114°C (H_2O); ^{1}H NMR ($CDCl_3$): δ 5.56 (s, 1H, N*H*), 7.50–7.61 (m, 3H), 7.73–7.75 (m, 2H) (C$_6$*H*$_5$); ^{13}C NMR (DMSO-d_6): δ 118.4 (*C*3 fx), 125.3 (*C*1 Ph), 128.4, 129.3, 131.1 (*C*4 Ph), 154.8 (*C*4 fx); ms: *m*/*z* 241 (M^+). *Anal*. Calcd. for $C_8H_7N_3O_4S$: C, 39.83; H, 2.92; N, 17.42. Found: C, 39.90; H, 2.94; N, 17.41.

***N*-Methyl-4-methylfuroxan-3-sulfonamide (11b).** HPLC (25/75 CH_3CN/H_2O + 0.1% CF_3COOH), second eluted. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, mp 48–50°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H, C*H*$_3$), 2.83 (d, 3H, C*H*$_3$), 5.47 (broad s., 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 12.2 (4-*C*H$_3$), 29.5, 117.2 (*C*3 fx), 152.9 (*C*4 fx); ms: *m*/*z* 193 (M^+). *Anal*. Calcd. for $C_4H_7N_3O_4S$: C, 24.87; H, 3.65; N, 21.75. Found: C, 24.83; H, 3.67; N, 21.51.

***N*,*N*-Diethyl-4-methylfuroxan-3-sulfonamide (13b).** HPLC (40/60 CH_3CN/H_2O; 20mL/min), second eluted. The obtained

solid was crystallized from hexane to give the title compound as a white solid, mp 92–93°C (hexane); ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 6H, 2CH_3), 2.53 (s, 3H, CH_3), 3.45 (q, 4H, 2CH_2); ^{13}C NMR ($CDCl_3$): δ 12.5 (4-*C*H_3), 14.4, 43.5, 118.5 (*C*3 fx), 152.7 (*C*4 fx); ms: *m*/*z* 235 (M^+). *Anal*. Calcd. for $C_7H_{13}N_3O_4S$: C, 35.74; H, 5.57; N, 17.86. Found: C, 35.69; H, 5.56; N, 17.72.

***N*-(4-Bromophenyl)-4-methylfuroxan-3-sulfonamide (15b).** HPLC (70/30 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min), second eluted. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, mp 114.5–115.5°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 7.11 (d, 2H), 7.43–7.50 (m, 3H) (C_6H_4 + N*H*); ^{13}C NMR ($CDCl_3$): δ 12.1 (4-*C*H_3), 117.2 (*C*3 fx), 125.2, 132.4, 133.1, 152.8 (*C*4 fx); ms: *m*/*z* 333/335 (M^+). *Anal*. Calcd. for $C_9H_8BrN_3O_4S$: C, 32.35; H, 2.41; N, 12.58. Found: C, 32.42; H, 2.42; N, 12.57.

***N*-(4-Bromophenyl)-4-phenylfuroxan-3-sulfonamide (16b).** HPLC (60/40 CH_3CN/H_2O + 0.1% CF_3COOH; 20 mL/min) second eluted. The obtained solid was crystallized from CCl_4 to give the title compound as a white solid, mp 158–159°C (CCl_4); ^{1}H NMR ($CDCl_3$): δ 7.02–7.07 (m, 2H), 7.41–7.60 (m, 7H) (C_6H_5, C_6H_4), 7.26 (s, 1H, N*H*); ^{13}C NMR ($CDCl_3$): δ 117.2, 121.3 (*C*3 fx), 124.4 (*C*1 Ph), 124.9, 128.7, 129.2, 131.8 (*C*4 Ph), 132.5, 133.0, 155.3 (*C*4 fx); ms: *m*/*z* 396/398 [$(M+H)^+$]. *Anal*. Calcd. for $C_{14}H_{10}BrN_3O_4S$: C, 42.44; H, 2.54; N, 10.61. Found: C, 42.31; H, 2.62; N, 10.54.

Ionization constants measurements. The ionization constants were determined by a potentiometric method using GLpK_a apparatus (Sirius Analytical Instruments, Forest Row, East Sussex, UK). The titrations were carried out under nitrogen atmosphere, at constant ionic strength ($I = 0.15M$ KCl) and temperature ($t = 25.0 \pm 0.5$°C). Ionization constants of **9a-c**, **10a-c**, and **11a-c**, were determined by at least three aqueous titration: solutions of the compounds (20 mL, about 1 m*M*) were initially acidified to pH 1.8 with 0.5*N* HCl and the solutions were then titrated with standardized 0.5*N* KOH to pH 10.0. Because of the low aqueous solubility, compounds of **12a**, **12c**, **15a-c**, and **16a-c** required titrations in methanol–water mixtures according to the following procedure. At least five different hydro-organic solutions of the compounds (20 mL, about 1 m*M* in 15–65 Wt % methanol) were titrated with the same protocol aforementioned. The apparent ionization constants in water–methanol mixtures (p_sK_as) were obtained and aqueous pK_a values were determined by extrapolation at 0% methanol using the Yasuda-Shedlovsky procedure [17].

Vasodilator activity. Thoracic aortas were isolated from male Wistar rats weighing 180–200 g. As few animals as possible were used. The purposes and the protocols of our studies have been approved by the Ministero della Salute, Rome, Italy. Experiments were performed according to procedures described earlier [18]. Results are expressed as $EC_{50} \pm$ SE (μ*M*). Responses were recorded by an isometric transducer connected to the MacLab System PowerLab (ADInstruments, Bella Vista, Australia). Addition of the drug vehicle (DMSO) had no appreciable effect on contraction level.

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