Study of Synthesis and Cardiovascular Activity of Some Furoxan Derivatives as Potential NO-Donors

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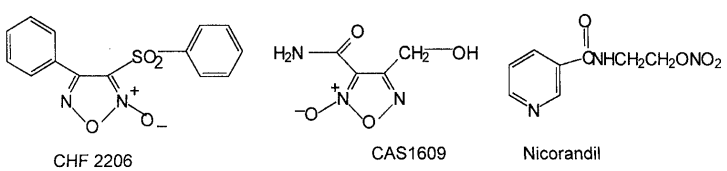
A series of hybrid molecules incorporating the furoxan and nicorandil moieties were designed as potential NO donors with cardiovascular and cerebrovascular activities. Thirty-six target molecules were successfully synthesized by conventional methods and characterized by infrared spectroscopy, ^{1}H-NMR spectroscopy and high resolution mass spectra. The compounds were tested for their effects on KCl-induced contraction of rabbit thoracic aorta whose endothelium was denuded. Eight compounds were found to reduce KCl-induced contraction by more than 30% at 10 μM. All except one of these compounds are characterized by the presence of electron withdrawing groups in the phenyl ring attached *via* an amide or ester linkage to the furoxan moiety. The nature of the terminal carbonyl linkage (ester or amide) and the length or type of the alkyl chain bridging the two carbonyl functions have little effect on the activity. One of the active compounds, *N*-(4-methoxy-benzoyl)-*N'*-[3-methylfuroxanyl-4-carbonyl)piperazine (17i) was tested for hypotensive effects on anaesthesized rats at 1.5 mg/kg, and found to demonstrate a gradual and sustained hypotensive effect. The results suggest that the furoxan-nicorandil derivatives are a useful lead in the design of NO-donor compounds for hypertension.

Key words furoxan derivatives; vasodilation; nitric oxide; NO-donor; synthesis; hypertension

Nitric oxide (NO) is an important messenger involved in many pathological and physiological processes which occur in the mammalian body. It has been shown to play a key role in neurotransmission, control of blood pressure and cellular defence mechanisms.[1] The increasing awareness of the involvement of NO in numerous bioregulatory pathways has also opened up new therapeutic avenues for organic nitrates and NO donors, and underscored the importance of such compounds in mimicking an endogenous NO-related response or substituting for an endogenous NO deficiency.[2] A variety of acute and chronic circulatory diseases are known which are associated with a marked degree of endothelial dysfunction and characterized by a significant attenuation of endothelial derived NO.[3,4] An emerging therapeutic strategy is to administer physiological amounts of NO in the bloodstream or at the site of the local tissue and injured cells in order to improve diminished supplies of NO for the maintenance of cardiovascular homeostasis. The furoxan ring system (1,2,5-oxadiazole-2-oxide, furazan oxide) has been widely used as an intermediate for the synthesis of various heterocyclic compounds,[5] owing to its mysterious structure or intricate chemistry. It has been reported to possess a wide spectrum of pharmacological activities, including vasodilatory activity.[6—12] Studies have shown that furoxan derivatives are NO donors,[10—16] which generate NO or related *N*-oxide species in a controlled manner. These findings have prompted the inclusion of the furoxan ring in the design of NO releasing drugs. The furoxan derivatives CAS 1609 and CHF 2206 are notable examples of furoxan derivatives which have demonstrated the success of such an approach (Fig. 1). They exert vasodilating activity with a pharmacological potency suggestive of NO donating pro-drugs (so-called NO donors).[3,16] CHF 2206 (3-phenylsulfonyl-4-phenylfuroxan) was able to inhibit rabbit aortic ring contraction induced by norepinephrine and KCl, and the activity was independent of endothelium integrity. CAS 1609 (2-hydroxymethyl-furoxan-3-carboxamide) relaxed both potassium-depolarized and phenylephrine-contracted guinea pig vessel strips in a concentration-dependent manner.

The combination of a nitrate moiety with another pharmacologically active substructure in a single molecule has recently received particular attention.[2,17,18] Nicorandil is an antianginal drug, which shares properties of K^+ channel openers and NO donors. It causes vascular smooth muscle relaxation *via* two main mechanisms: increasing membrane K^+ conductance through the opening of ATP-dependent K^+ channels leading to hyperpolarization and releasing NO elevating cyclic GMP levels by stimulating soluble guanylate cyclase.[17] Nicorandil may be the prototype of the hybrid drugs with K^+ channel opening properties mixed with NO-dependent vasodilating activities. Structurally, it is a nicotinamide derivative with a nitrate group in its chemical structure (Fig. 1). The O–NO_2 moiety is responsible for the group's action as nitrates and also influences their potency as K^+-chan-



CHF 2206 CAS1609 Nicorandil

Fig. 1. Structures of CHF 2206, CAS 1609 and Nicorandil

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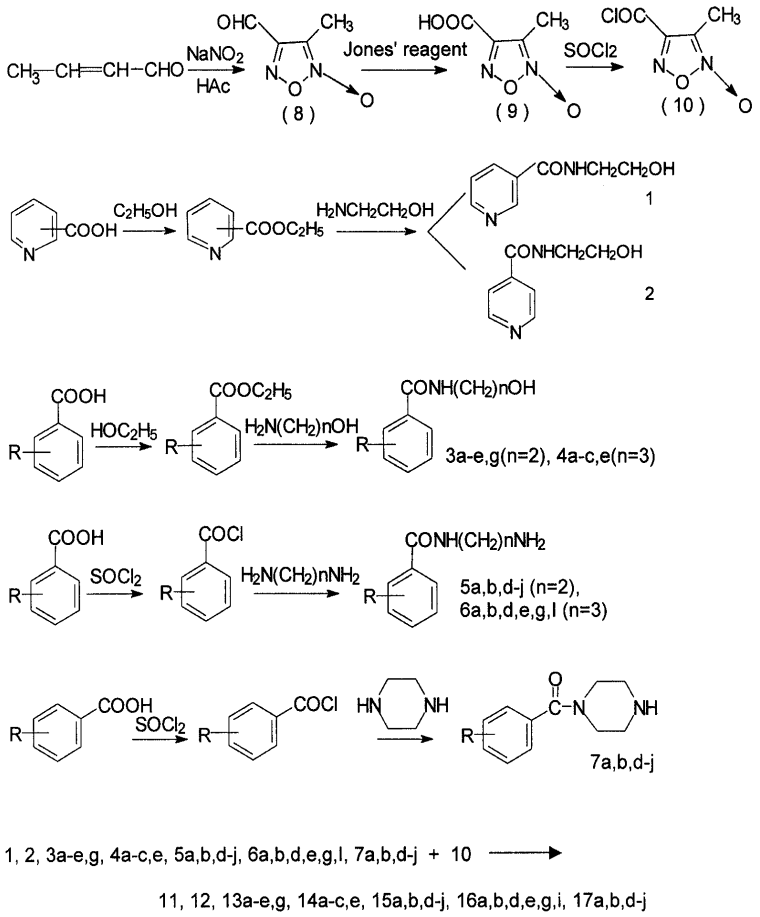


Chart 1

nel activators.

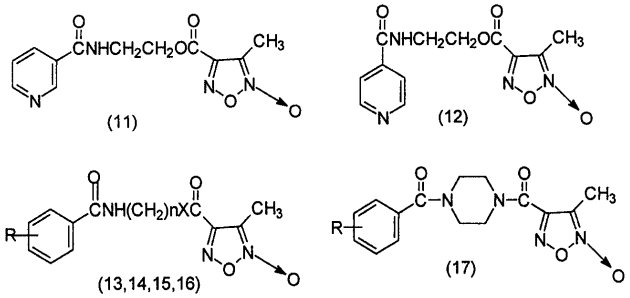
The synthesizing of hybrid molecules of furoxan and nicorandil derivatives may prove to be a useful approach in moderating the NO releasing properties,[18,19] so as to achieve an ideal cardiovascular drug with good selectivity, efficiency, acceptable duration of action and low toxicity.

Based on this idea, we synthesized in the present paper a series of "hybrid" drugs designed by linking the furoxan ring to nicorandil analogues and investigated their NO donating properties. The compounds are evaluated for their ability to inhibit KCl-induced contraction of rabbit aortic strips which have been denuded of endothelium. Eight compounds were identified to possess good vasodilatory activity and one of them was further tested for its hypotensive effects in anaesthesized rats. This compound was found able to significantly reduce blood pressure 3 h after administration. Its hypotensive effects can prevail for a further 3 h. The results indicate that the present approach of molecular hybridization is a viable step in designing active NO releasing compounds.

Results and Discussion

Chemistry The furoxan-nicorandil derivatives were synthesized according to the pathways shown in Chart 1. 3-Methylfuroxan-4-carbaldehyde (**8**) was synthesized from the reaction of dinitrogen trioxide (generated from sodium nitrite and acetic acid) on crotonaldehyde.[19,20] The aldehyde was oxidized to the acid (3-methylfuroxan-4-carboxylic acid (**9**) using Jones' reagent, and the resulting acid was converted to the reactive acid chloride using thionyl chloride. The acid

Table 1. Chemical Structures of Synthesized Furoxan Derivatives **11**—**17**



Compounds					R
X=O		X=NH			
13 (n=2)	**14** (n=3)	**15** (n=2)	**16** (n=3)	**17**	
13a	**14a**	**15a**	**16a**	**17a**	3-NO_2
13b	**14b**	**15b**	**16b**	**17b**	4-NO_2
13c	**14c**				3,4-di-NO_2
13d		**15d**	**16d**	**17d**	3-Cl
13e	**14e**	**15e**	**16e**	**17e**	4-Cl
		15f		**17f**	3-Br
13g		**15g**	**16g**	**17g**	4-Br
		15h		**17h**	3-OCH_3
		15i	**16i**	**17i**	4-OCH_3
		15j		**17j**	H

Table 2. Physical Data of Synthesized Compounds

Compound	Yield (%)	mp (°C)	IR (cm^{-1})	^{1}H-NMR (δ ppm)	HR-MS
11	54.5	112—114	3250, 3060 (N-H); 1730, 1650 (C=O); 1100 (O=C−O)	8.98 (d,1H, pyridine-C_2H), 8.75—8.66 (s+dd, 2H, pyridine-C_6-H, CONH), 8.23—8.09 (tt, 1H, pyridine-C_4-H), 7.56—7.34 (q, 1H, pyridine-C_5-H), 4.61—4.48 (t, 2H, CH_2OCO), 3.79—3.60 (q, 2H, $NHCH_2$), 2.26 (S, 3H, CH_3)	Formula $C_{12}H_{12}N_4O_5$ $(M+H)^+$ Calcd 293.088047. Found 293.089550. MS (SCI, *m/z*):293 (MH^+, base peak), 149 ($C_5H_4NCONHCH_2CH_2^+$), 121 ($C_5H_4NCONH^+$)
12	50.5	168—170	3200, 3050 (N-H); 1750, 1650 (C=O); 1100 (O=C−O)	8.85 (s, 1H, CONH), 8.37—8.67 (dd, 2H, pyridine-C_2,C_6-2H), 7.79—7.72 (dd, 2H, pyridine-C_3, C_5-2H), 4.60—4.54 (t, 2H, CH_2OCO), 3.80—3.70 (q, 2H, $NHCH_2$), 2.31 (s, 3H, CH_3)	Formula $C_{12}H_{12}N_4O_5$ $(M+H)^+$ Calcd 293.088047. Found 293.088075. MS (SCI, *m/z*): 293 (MH^+, base peak), 214 ($CONHCH_2CH_2$−Furoxan), 149 ($C_5H_4NCONHCH_2CH_2^+$)
13a	33.2	112—114	3260, 3100 (N-H); 1730, 1640 (C=O); 1120 (O=C−O)	8.95 (s, br, 1H, CONH), 8.789—8.748 (t, 1H, ArH), 8.392—8.253 (m, 2H, ArH), 7.768—7.680 (q, 1H, ArH), 4.681—4.558 (t, 2H, CH_2OCO), 3.825—3.762 (m, 2H, N-CH_2C), 2.332 (s, 3H, CH_3)	Formula $C_{13}H_{12}N_4O_7$ $(M+H)^+$ Calcd 337.077877. Found 337.079630. MS (SCI, *m/z*): 337 (MH^+), 193 ($C_6H_4NO_2CONHCH_2CH_2^+$) 176 ($C_6H_4NO_2CONHCH_2CH^+$), 150 (C_6H_4-NO_2CO^+), 89 ($C_6H_5Cl^+$)
13b	36.6	122—124	3300, 3100 (N-H); 1730, 1630 (C=O); 1100 (O=C−O)	8.321—7.996 (m, 4H, ArH), 4.640 (t, 2H, CH_2OCO), 3.95—3.75 (m, 2H, NCH_2C), 2.362 (s, 3H, CH_3)	Formula $C_{13}H_{12}N_4O_7$ $(M+H)^+$ Calcd 337.077877. Found 337.079630. MS (SCI, *m/z*): 193 ($C_6H_4NO_2NHCH_2CH_2^+$), 176 ($C_6H_4NO_2$-$CONHCH_2CH^+$).
13c	30.6	172—174	3300, 3100 (N-H); 1740, 1650 (C=O); 1100 (O=C−O)	9.35 (br, 1H, CONH), 9.160—9.043 (m, 3H, ArH), 4.626—4.563 (t, 2H, CH_2OCO), 3.836—3.779 (q, 2H, NCH_2C), 2.326 (s, 3H, CH_3)	Formula $C_{13}H_{11}N_5O$ $(M+H)^+$ Calcd 382.062956. Found 382.061212. MS (SCI, *m/z*): 382 (MH^+), 238 (base peak, $C_6H_3N_2O_4CO$ $NHCH_2$–CH_2^+), 193 ($C_6H_4NO_2$ $CONHCH_2$-CH_2^+)
13d	20.2	96—98	3250, 3080 (N-H); 1730, 1630 (C=O); 1100 (O=C−O)	8.60 (br, 1H, CONH), 7.877—7.789 (m, 2H, ArH), 7.462—7.370 (m, 2H, ArH), 4.648—4.525 (t, 2H, CH_2OCO), 3.779—3.719 (m, 2H, NCH_2C), 2.324 (s, 3H, CH_3)	Formula $C_{13}H_{12}N_3O_5Cl$ $(M+H)^+$ Calcd 326.053825. Found 326.056041. MS (SCI, *m/z*): 326 (MH^+), 214 ($CONHCH_2CH_2$Furoxan$^+$), 182 (base peak, $C_6H_4ClCONHCH_2CH_2^+$), 139 ($C_6H_4ClCO^+$), 89 ($C_6H_5CO^+$)
13e	23.9	152—154	3400, 3100 (N-H); 1730, 1640 (C=O); 1100 (O=C-O)	8.50 (br, 1H, CONH), 7.887—7.792 (m, 2H, ArH), 7.438—7.343 (m, 2H, ArH), 4.642—4.520 (t, 2H, CH_2COC), 3.776—3.716 (m, 2H, NCH_2), 2.310 (s, 3H, CH_3)	Formula $C_{13}H_{12}N_3O_5Cl$ $(M+H)^+$ Calcd 326.053825. Found 326.053883. MS (SCI, *m/z*): 326 (MH^+), 182 (base peak, $C_6H_4ClCONH$-$CH_2CH_2^+$), 139 (C_6H_4Cl CO^+)
13g	22.6	160—162	3400, 3080 (N-H); 1740, 1650 (C=O); 1100 (O=C−O)	8.50 (br, 1H, CONH), 7.817—7.490 (m, 4H, ArH), 4.651—4.528 (t, 2H, CH_2COC), 3.787—3.727 (m, 2H, NCH_2), 2.318 (s, 3H, CH_3)	Formula $C_{13}H_{12}N_3O_5Br$ $(M+H)^+$ Calcd 370.003309. Found 370.002949. MS (SCI, *m/z*): 370 (MH^+), 226 (base peak, $C_6H_4BrCONH$-$CH_2CH_2^+$), 183 ($C_6H_4BrCO^+$)
14a	19.9	114—116	3300, 3080 (N-H); 1730, 1640 (C=O); 1100 (O=C−O)	8.781—8.759 (t, 1H, ArH), 8.60 (br, 1H, CONH), 8.351—8.247 (m, 2H, ArH), 7.727—7.588 (q, 1H, ArH), 4.601—4.463 (t, 2H, CH_2O), 3.610—3.547 (m, 2H, NCH_2C), 2.373 (s, 3H, CH_3), 2.212—2.070 (q, 2H, CCH_2C).	Formula $C_{14}H_{14}N_4O_7$ $(M+H)^+$ Calcd 351.093527. Found 351.094320. MS (SCI, *m/z*): 351 (MH^+), 207 (base peak, $C_6H_4NO_2CONH$ $(CH_2)_3^+$), 150 ($C_6H_4NO_2$ CO^+)
14b	22.6	106—108	3300 (N-H); 1730, 1640 (C=O); 1100 (C=O)	8.318—7.966 (m, 4H, ArH), 4.498 (t, 2H, CH_2OCO), 3.50 (m, 2H, NCH_2), 2.343 (s, 3H, CH_3), 2.05 (t, 2H, CCH_2C)	Formula $C_{14}H_{14}N_4O_7$ $(M+H)^+$ Calcd 351.093527. Found 351.093360. MS (SCI, *m/z*): 351 (MH^+), 207 (base peak, $C_6H_4NO_2CONH$ $(CH_2)_3^+$), 150 ($C_6H_4NO_2$ CO^+)
14c	20.5	114—116	3380, 3080 (N-H); 1740, 1640 (C=O); 1100 (O=C−O)	9.233—9.075 (m, 3H, ArH), 4.618—4.479 (t, 2H, CH_2OCO), 3.659—3.593 (m, 2H, NCH_2), 2.247—2.103 (t, 2H, CCH_2C)	Formula $C_{14}H_{13}N_5O_9$ $(M+H)^+$ Calcd 396.078606. Found 396.079600. MS (SCI, *m/z*): 396 (MH^+), 252 (base peak, $C_6H_3N_2O_4CO$-$NH(CH_2)_3^+$), 195 ($C_6H_3N_2O_4CO^+$)
14e	18.8	108—110	3400, 3100 (N-H); 1730, 1640 (C=O); 1100 (O=C−O)	8.60 (br, 1H, CONH), 7.886—7.464 (m, 4H, ArH), 3.359—3.234 (m, 4H, NCH_2, CH_2N), 2.253 (s, 3H, CH_3), 1.866—1.713 (m, 2H, CCH_2C)	Formula $C_{14}H_{14}N_3O_5Cl$ $(M+H)^+$ Calcd 340.078825; Found 340.078883. MS (SCI, *m/z*): 340 (MH^+), 196 (base peak, $C_6H_4ClCONH$-$(CH_2)_3^+$), 139 (C_6H_4Cl CO^+)

Table 2. (Continued)

Compound	Yield (%)	mp (°C)	IR (cm^{-1})	^{1}H-NMR (δ ppm)	HR-MS
15a	20.6	190	3300, 3100 (N-H); 1660, 1640 (C=O)	8.787—8.743 (t, 1H, ArH), 8.381—8.247 (m, 2H, ArH), 7.740—7.566 (q, 1H, ArH), 3.642 (br, 4H, NCH_2–CH_2N), 2.359 (s, 3H, CH_3)	Formula $C_{13}H_{13}N_5O_6$ $(M+H)^+$ Calcd 336.093861. Found 336.095230. MS (SCI, *m/z*): 336 (MH^+, base peak), 318 ($MH+H_2O$), 236 ($C_6H_4NO_2$ $CONHCH_2CH_2NH$ CO^+), 170 (CH_2CH_2–Furoxan$^+$)
15b	23.3	154—155	3300 (N-H); 1670, 1630 (C=O)	8.70 (br, 1H, CONH), 8.45 (br, 1H,CONH), 8.299—8.010 (m, 4H, ArH), 3.642 (br, 4H, NCH_2CH_2N), 2.356 (s, 3H, CH_3)	Formula $C_{13}H_{13}N_5O_6$ $(M+H)^+$ Calcd 336.093861. Found 336.095859. MS (SCI, *m/z*): 336 (MH^+, base peak), 318 (MH^+H_2O), 236 ($C_6H_4NO_2CONC(CH_2)_2NHCO^+$), 170 ($CH_2$-$CH_2$–Furoxan), 150 ($C_6H_4NO_2CO^+$), 104 ($C_6H_4CO^+$)
15d	17.5	154—156	3300, 3060 (N-H); 1670, 1630 (C=O)	8.75 (br, m, CONH), 8.25 (br, 1H, CONH), 7.868—7.729 (m, 2H, ArH), 7.449—7.356 (m, 2H, ArH), 3.599—3.572 (br, 4H, NCH_2CH_2N), 2.340 (s, 3H, CH_3)	Formula $C_{13}H_{13}N_4O_4Cl$ $(M+H)^+$ Calcd 325.069809. Found 325.071878. MS (SCI, *m/z*): 325 (MH^+), 307 (MH^+H_2O), 170 (CH_2CH_2–Furoxan$^+$), 139 (base peak, $C_6H_4ClCO^+$), 111 ($C_6H_4Cl^+$)
15e	24.5	122—124	3350 (N-H); 1670, 1630 (C=O)	8.55 (br, 1H, CONH), 8.00 (br, 1H, CONH), 7.857—7.759 (m, 2H, ArH), 7.416—7.318 (m, 2H, ArH), 3.612 (br, 4H, NCH_2–CH_2N), 2.348 (s,3H,CH_3)	Formula $C_{13}H_{13}N_4O_4Cl$ $(M+H)^+$ Calcd 325.069809. Found 325.071709. MS (SCI, *m/z*): 325 (MH^+), 307 ($MH+H_2O$), 139 (base peak, $C_6H_4ClCO^+$), 111 ($C_6H_4Cl^+$)
15f	15.7	162—168	3300 (N-H); 1670, 1630 (C=O)	8.85 (br, 1H, CONH), 8.35 (br, 1H, CONH), 8.018—7.318 (m, 4H, ArH), 3.640 (br, 4H, NCH_2CH_2N), 2.351 (s, 3H, CH_3)	Formula $C_{13}H_{13}N_4O_4Br$ $(M+H)^+$ Calcd 369.019293. Found 369.020400. MS (SCI, *m/z*): 369 (MH^+), 351 (MH^+H_2O), 183 (base peak, $C_6H_4ClCO^+$), 170 (CH_2CH_2–Furoxan$^+$), 155 ($C_6H_4Br^+$)
15g	20.5	196—198	3350 (N-H); 1670 (C=O)	8.70 (br, 1H, CONH), 7.795—7.468 (m, 4H, ArH), 3.569 (br, 4H, NCH_2–CH_2N), 2.343 (s, 3H, CH_3).	Formula $C_{13}H_{13}N_4O_4Br$ $(M+H)^+$ Calcd 369.019293. Found 369.020727. MS (SCI, *m/z*): 369 (MH^+), 183 (base peak, $C_6H_4BrCO^+$), 170 (CH_2CH_2–Furoxan$^+$), 155 ($C_6H_4Br^+$)
15h	14.5	106—108	3300 (N-H), 1670, 1630 (C=O)	8.65 (br, 1H, CONH), 8.15 (br, 1H, CONH), 7.85—6.95 (m, 4H, ArH), 3.836 (s, 3H, OCH_3), 3.659—3.612 (br, 4H, NCH_2–CH_2N), 2.356 (s, 3H, CH_3)	Formula $C_{14}H_{16}N_4O_5$ $(M+H)^+$ Calcd 321.119347. Found 321.121080. MS (SCI, *m/z*): 321 (MH^+), 303 ($MH+H_2O$), 170 (CH_2CH_2–Furoxan$^+$), 151 ($C_6H_4OCH_3C^+$), 135 (base peak, $C_6H_4OCH_3$ CO^+), 107 ($C_6H_4OCH_3^+$)
15i	23.6	128—130	3300 (N-H); 1660, 1630 (C=O)	7.789—7.691 (m, 2H, ArH), 6.958—6.858 (m, 2H, ArH), 3.844 (s, 3H, OCH_3), 3.716—3.681 (br, 4H, NCH_2CH_2N), 2.365 (s, 3H, CH_3)	Formula $C_{14}H_{16}N_4O_5$ $(M+H)^+$ Calcd 321.119347. Found 321.117630. MS (SCI, *m/z*): 321 (MH^+), 303 ($MH+H_2O$), 170 (CH_2CH_2–Furoxan$^+$), 151 ($C_6H_4OCH_3C^+$), 135 (base peak, $C_6H_4OCH_3CO^+$), 107 ($C_6H_4OCH_3^+$)
15j	13.6	164—166	3400, 3310 (N-H); 1670, 1640 (C=O)	8.72 (br, 1H, CONH), 8.06 (br, 1H, CONH), 7.896—7.381 (m, 5H, ArH), 3.629—3.615 (br, 4H, CH_2CH_2), 2.348 (s, 3H, CH_3)	Formula $C_{13}H_{14}N_4O_4$ $(M+H)^+$ Calcd 291.08782. Found 291.08510. MS (SCI, *m/z*): 291(MH^+), 273 (MH^+H_2O), 170 (CH_2CH_2–Furoxan$^+$), 134 (C_6H_5CONH CH_2^+), 105 (base peak, C_6H_5 CO^+), 77 ($C_6H_5^+$)
16a	18.6	152—154	3360, 3320 (N-H); 1670, 1640 (C=O)	8.784 (t, 1H, ArH), 8.394—8.280 (q, 2H, ArH), 7.739—7.550 (t,1H,ArH), 3.501 (br, 4H, NCH_2CH_2N), 2.397 (s, 3H, CH_3), 1.95—1.85 (m, 2H, CCH_2C)	Formula $C_{14}H_{15}N_5O_6$ $(M+H)^+$ Calcd 350.109511. Found 350.108110. MS (SCI, *m/z*): 350 (MH^+), 332 (MH^+H_2O), 250 ($C_6H_4NO_2$ $CONH(CH_2)_3NHCO^+$), 150 (base peak, $C_6H_4NO_2CO^+$), 104 ($C_6H_4CO^+$), 76 ($C_6H_4^+$)
16b	21.8	156—158	3350 (N-H); 1660, 1620 (C=O)	8.386—8.288 (m, 2H, ArH), 8.013—7.912 (m, 2H, ArH), 4.280—4.117 (t, 2H, CH_2H), 3.610—3.495 (q, 2H, NCH_2), 2.320 (s, 3H, CH_3), 2.182 (m, 2H, CCH_2C)	Formula $C_{14}H_{15}N_5O_6$ $(M+H)^+$ Calcd 336.109511. Found 350.108410. MS (SCI, *m/z*): 350 (MH^+), 250 ($C_6H_4NO_2CONC$ $((CH_2)_3$-$NHCO^+$), 207 (C_6H_4CONH-$(CH_2)_3^+$), 184 $(CH_2)_3$–Furoxan$^+$), 150 (base peak, $C_6H_4NO_2CO^+$), 104 ($C_6H_4CO^+$), 76 ($C_6H_4^+$)

Table 2. (Continued)

Compound	Yield (%)	mp (°C)	IR (cm^{-1})	^{1}H-NMR (δ ppm)	HR-MS
16d	19.6	154—156	3360, 3260 (N-H); 1670, 1630 (C=O)	8.95 (br, 1H, CONH), 8.45 (br, 1H, CONH), 7.896—7.454 (m, 4H, ArH), 3.359—3.234 (m, 4H, NCH_2, CH_2N), 2.253 (s, 3H, CH_3), 1.866—1.713 (m, 2H, CCH_2C)	Formula $C_{14}H_{15}N_4O_4Cl$ $(M+H)^+$ Calcd 339.094809. Found 339.096818. MS (SCI, *m/z*): 339 (MH^+), 321 ($MH+H_2O$), 184 ($(CH_2)_3$–Furoxan$^+$), 139 (base peak, $C_6H_4ClCO^+$), 111 ($C_6H_4Cl^+$)
16e	24.5	166—168	3400, 3270 (N-H); 1670, 1640 (C=O)	8.95 (br, 1H, CONH), 8.45 (br, 1H, CONH), 7.896—7.454 (m, 4H, ArH), 3.359—3.234 (m, 4H, NCH_2CH_2N), 2.253 (s, 3H, CH_3), 1.866—1.713 (m, 2H, CCH_2C)	Formula $C_{14}H_{15}N_4O_4Cl$ $(M+H)^+$ Calcd 339.094809. Found 339.096709. MS (SCI, *m/z*): 339 (MH^+), 321 (MH^+H_2O), 139 (base peak, $C_6H_4ClCO^+$), 111 ($C_6H_4Cl^+$)
16g	21.5	188—190	3400, 3260 (N-H); 1670, 1640 (C=O)	8.95 (br, 1H, CONH), 8.45 (br, 1H, CONH), 7.844—7.533 (m, 4H, ArH), 3.343 (m, 4H, NCH_2, CH_2N), 2.302 (s, 3H, CH_3), 1.822 (m, 2H, CCH_2C)	Formula $C_{14}H_{15}N_4O_4Br$ $(M+H)^+$ Calcd 383.034943. Found 383.033280. MS (SCI, *m/z*): 383 (MH^+), 365 (MH^+H_2O), 256 ($C_6H_4BrCONHCH(CH_2)_3NHCO^+$), 187 ($(CH_2)_3$–Furoxan$^+$), 183 (base peak, $C_6H_4BrCO^+$), 155 ($C_6H_4Br^+$)
16i	11.5	140—142	3400, 3240 (N-H); 1670, 1630 (C=O)	8.94 (br,1H,CONH), 8.14 (br, 1H, CONH), 7.868—7.773 (m, 2H, ArH), 6.964—6.866 (m, 2H, ArH), 3.833 (s, 3H, OCH_3), 3.457—3.305 (m, 4H, NCH_2–CH_2N), 2.318 (s, 3H, CH_3), 1.822 (m, 2H, CCH_2C)	Formula $C_{15}H_{18}N_4O_5$ $(M+H)^+$ Calcd 335.134997. Found 335.133950. MS (SCI, *m/z*): 335 (MH^+), 317 ($MH+H_2O$), 184 ($(CH_2)_3$–Furoxan$^+$), 135 (base peak, $C_6H_4OCH_3CO^+$),
17a	28.6	108—110	1640 (C=O)	8.288 (m, 2H, ArH), 7.754—7.656 (m, 2H, ArH), 3.820 (br, 8H, NC_4H_8N), 2.299 (s, 3H, CH_3). 107 ($C_6H_4OCH_3^+$)	Formula $C_{15}H_{15}N_5O_6$ $(M+H)^+$ Calcd 362.109511. Found 362.107139. MS (SCI, *m/z*): 362 (MH^+, base peak), 344 (MH^+H_2O), 262 ($C_6H_4NO_2CONC_4H_8N^+$), 150 ($C_6H_4NO_2$-CO^+)
17b	29.9	170—172	1640, 1630 (C=O)	8.356—8.258 (m, 2H, ArH),7.661—7.561 (m, 2H, ArH), 3.790 (br, 8H, NC_4H_8N), 2.299 (s, 3H, CH_3)	Formula $C_{15}H_{15}N_5O_6(M+H)^+$ Calcd 362.109511. Found 362.111748. MS (SCI, *m/z*): 362 (MH^+, base peak), 344 (MH^+H_2O), 262 ($C_6H_4NO_2CONC_4H_8NCO^+$), 150 ($C_6H_4NO_2CO^+$)
17d	19.5	60—62	1640, 1630 (C=O)	7.441—7.280 (m, 4H, ArH), 3.770 (br, 8H, NC_4H_8N), 2.294 (s, 3H, CH_3)	Formula $C_{15}H_{15}N_4O_4Cl$ $(M+H)^+$ Calcd 351.08459. Found 351.085840. MS (SCI, *m/z*): 351 (MH^+), 333 (MH^+H_2O), 139 (base peak, $C_6H_4ClCO^+$), 111 ($C_6H_4Cl^+$)
17e	22.6	132—134	1640, 1630 (C=O)	7.40 (s, 4H, ArH), 3.88—3.77 (br, 8H, NC_4H_8N), 2.29 (s, 3H, CH_3)	Formula $C_{15}H_{15}N_4O_4Cl$ $(M+H)^+$ Calcd 351.08459. Found 351.085840. MS (SCI, *m/z*): 351 (MH^+), 333 (MH^+H_2O), 139 (base peak, $C_6H_4ClCO^+$), 111 ($C_6H_4Cl^+$)
17f	20.6	78—80	1650, 1640 (C=O)	7.566—7.303 (m, 4H, ArH), 3.773 (br, 8H, NC_4H_8N), 2.288 (s, 3H, CH_3)	Formula $C_{15}H_{15}N_4O_4Br$ $(M+H)^+$ Calcd 395.034943. Found 395.0331790. MS (SCI, *m/z*): 395 (MH^+), 377 (MH^+H_2O), 267 ($C_6H_4BrCONC_4H_8N^+$), 211 (NC_4H_8N–Furoxan$^+$), 183 (base peak, $C_6H_4BrCO^+$), 155 ($C_6H_4Br^+$)
17g	29.8	156—158	1650, 1630 (C=O)	7.645—7.310 (m, 4H, ArH), 3.798 (m, 8H, NC_4H_8N), 2.294 (s, 3H, CH_3)	Formula $C_{15}H_{15}N_4O_4Br$ $(M+H)^+$ Calcd 395.034943. Found 395.033597. MS (SCI, *m/z*): 395 (MH^+), 377 (MH^+H_2O), 267 ($C_6H_4BrCONC_4H_8N^+$), 183 (base peak, $C_6H_4BrCO^+$), 155 ($C_6H_4Br^+$)
17h	19.5	112—114	1640, 1630 (C=O)	7.441—6.931 (m, 4H, ArH), 3.830 (br, 8H, NC_4H_8N), 2.286 (s, 3H, CH_3)	Formula $C_{16}H_{18}N_4O_5$ $(M+H)^+$ Calcd 347.134997. Found 347.134790. MS (SCI, *m/z*): 347 (MH^+), 135 (base peak, $C_6H_4OCH_3CO^+$), 107 ($C_6H_4OCH_3^+$), 77 ($C_6H_5^+$)
17i	21.2	104—106	1650, 1630 (C=O)	7.545—7.299 (m, 2H, ArH), 6.975—6.879 (m, 2H, ArH), 3.841—3.773 (m, 3H+8H, $OCH_3+NC_4H_8N$), 2.286 (s, 3H, CH_3)	Formula $C_{16}H_{18}N_4O_5$ $(M+H)^+$ Calcd 347.134997. Found 347.137267. MS (SCI, *m/z*): 347 (MH^+), 135 (base peak, $C_6H_4OCH_3$-CO^+)
17j	16.6	118—120	1650, 1630 (C=O)	7.427 (s, 5H, ArH), 3.762—3.563 (m, 8H, NC_4H_8N), 2.283 (s, 3H, CH_3)	Formula $C_{15}H_{16}N_4O_4$ $(M+H)^+$ Calcd 317.124432. Found 317.124366. MS (SCI, *m/z*): 317 (MH^+, base peak), 105 ($C_6H_5CO^+$)

chloride (**10**) was reacted quickly with the following alcohols (**1**, **2**, **3a**—**e**, **g**; **4a**—**c**, **e**) and amines (**5a**, **b**, **d**—**j**; **6a**, **b**, **d**, **e**, **g**, **i**; **7a**, **b**, **d**—**j**) to give the desired compounds (**11**; **12**; **13a**—**e**, **g**; **14a**—**c**, **e**; **15a**, **b**, **d**—**j**; **16a**, **b**, **d**, **e**, **g**, **i**; **17a**, **b**, **d**—**j**) (Table 1).

The alcohols *N*-(2-hydroxyethyl)nicotinamide (**1**) and *N*-(2-hydroxyethyl)iso-nicotinamide (**2**) were synthesized by reacting the ethyl esters of nicotinic acid and isonicotinic acid with ethanolamine in chloroform. The alcohols in the **3**(**a**—**e**, **g**) series are *N*-(2-hydroxyethyl)benzamides, with mono- or di-substitution on the phenyl ring. The substituents on the ring were predominantly electron withdrawing groups (nitro, chloro, bromo) at the 3, 4 or 3, 4 positions, with the exception of the methoxy substituent. These were prepared from the reaction of ethanolamine and the ethyl ester of the substituted benzoic acid in refluxing chloroform. The alcohols in the **4**(**a**—**c**, **e**) series are ring substituted *N*-(3-hydroxypropyl)-benzamides and these were prepared from the reaction of propanolamine and the ethyl ester of the substituted benzoic acid in refluxing chloroform. The amines in series **5**, **6**, **7** are substituted *N*-(2-aminoethyl)benzamides, *N*-(3-aminopropyl)-benzamides and *N*-benzoylpiperazines, respectively. They were prepared from the reaction of ethylenediamine, 1,3-diaminopropane or piperazine with substituted benzoyl chlorides. The main difficulty encountered in the synthesis of these compounds is the reactivity of the amino groups in ethylenediamine, diaminopropane and piperazine, resulting in acylation of both amino groups by acid chloride. Various approaches can be used to prevent this from happening: one of the amino groups can be protected by formylation or with an ethoxycarbonyl group, or by conversion to a salt. All of these methods necessitate additional reaction steps and careful control of reaction conditions. Alternatively, the diamine may be titrated with the acyl chloride to ensure that the reaction is terminated only after 1 eq of the reagent has been consumed, or by reacting the diamine with the substituted benzoic acid using dicyclohexylcarbodiimide (DCC) as condensing agent. However, both approaches present considerable difficulties and it was not possible to obtain the monoacylated product by these techniques; this may be due to the fact that both amino groups are of very similar reactivity. It was subsequently found that the problem could be averted by converting the diamino compound into the monoamine salt form, or by carrying out the reaction in a weakly acidic solvent like acetic acid which serves to reduce the nucleophilicity of the amino group by salt formation. After numerous trials, it was found that monoacylation could be achieved if the reaction was carried out using a ratio of 2 parts acyl chloride to 3 parts diamine compound in acetic acid as solvent, and at room temperature. The monoacylated compounds were obtained as hydroscopic solids which were used immediately for the next step of the reaction.

Condensation of the alcohols (**1**, **2**, **3a**—**e**, **g**, **4a**—**c**, **e**) and amines (**5a**, **b**, **d**—**j**, **6a**, **b**, **d**, **e**, **g**, **i**; **7a**, **b**, **d**—**j**) with the furoxan (**10**) was carried out in either chloroform or dichloromethane in the presence of triethylamine, which served a catalytic function or reacted with HCl released during the reaction. The final compounds were characterized by IR, ^{1}H-NMR, and high resolution mass spectroscopy (HR-MS), and the analytical results were compatible with the proposed structures (Table 2).

Table 3. Inhibitory Effects of Furoxan Derivatives on Rabbit Aortia Strips Precontracted with KCl

Compound	Concentration (μM)	Inhibitory percentage (%, ±SE)			
		Low [K^+] (30 mM)		High [K^+] (80 mM)	
11	10	24.5	±3.1	0	
12	10	12.1	±14.8	0	
13a	10	31.9	±15.3	0	
13b	10	16.3	±8.3	3.0	±3.5
13c	10	16.4	±11.6	0	
13d	10	3.9	±3.9	3.0	±0.5
13e	10	0.4	±0.8	2.7	±4.1
13g	10	25.7	±24.8	0	
14a	10	12.4	±6.5	4.4	±1.3
14b	10	0.9	±1.6	1.3	±1.5
14c	10	30.3	±17.0	1.1	±2.0
14e	10	24.8	±4.4	2.1	±2.8
15a	10	34.8	±22.3	6.0	±7.1
15b	10	0		0.4	±0.7
15d	10	24.4	±17.7	9.2	±2.9
15e	10	30.4	±21.1	1.9	±2.4
15f	10	3.8	±4.8	0	
15g	10	39.6	±1.4	5.6	±2.3
15h	10	25.2	±4.9	2.5	±3.3
15i	10	13.1	±18.9	0.2	±0.4
15j	10	16.0	±12.9	0	
16a	10	40.1	±9.8	0.5	±0.8
16b	10	22.4	±7.5	0	
16e	10	40.6	±9.4	0.2	±0.4
16g	10	17.7	±7.9	0	
16i	10	28.7	±19.7	0.8	±1.7
17a	10	13.9	±13.8	2.2	±3.6
17b	10	15.6	±6.7	0	
17e	10	24.6	±12.2	5.2	±1.0
17f	10	28.8	±23.6	2.3	±3.9
17g	10	21.0	±10.7	4.2	±3.9
17h	10	0		0	
17i	10	36.3	±19.2	0.2	±0.4
17j	10	28.9	±23.8	0	

(Notes: Biological data are not available for compounds **16d** and **17d**).

Structure–Activity Relationship To investigate the vasorelaxing action of the synthesized compounds, different KCl-induced contraction systems were proposed. The inhibitory effect at high KCl concentration (80 mM) was not strong and the highest inhibition was only 9.2±2.9. Thus, a low KCl concentration (30 mM) system was used, and it was found that most of the compounds demonstrated the ability to cause a relaxation in the aorta precontracted with KCl; the highest inhibition was 40.6±9.4. The pharmacological data are shown in Table 3. Eight compounds reduced the KCl (30 mM)-induced contraction by at least 30%. They were **13a**, **14c**, **15a**, **15e**, **15g**, **16a**, **16e**, **17i**, all are substituted phenyl derivatives. The pyridyl derivatives **11** and **22** demonstrated significantly less activity. Of the 8 substituted phenyl derivatives, there is a significant preponderance of rings substituted with electron withdrawing groups (nitro or halogen) at the *meta* and/or *para* positions. The only exception is **17i** which has an electron donating methoxy function at the *para* position. Other than this feature, the presence of an amide or ester function in the side chain, the number of methylene units (2 or 3) between the carbonyl groups or the presence of a piperazine ring did not appear to be important determinants of activity.

Following the demonstration of functional vasodilatory ac-

tivity on the thoracic aorta whose endothelium was denuded, the effects of the compounds were investigated on the blood pressure of anaesthesized rats. Compound **17i** was chosen as a representative compound for this investigation and was found to cause a gradual reduction in the blood pressure (systolic, diastolic and mean arterial pressures) of the animal, which reached a plateau after 3 h. The reductions in these three arterial pressures were 30, 20 and 26 mmHg, respectively, after 3 h. The reduction in blood pressure was maintained over a period of 6 h thereafter. Therefore, it can be concluded that **17i** demonstrates a gradual and sustained hypotensive action which may be related to a measured release of NO from the furoxan moiety. This is a desirable feature which could be exploited in the drug design of potential NO donors.

Conclusion

Thirty six furoxan-nicorandil derivatives have been synthesized successfully by conventional chemical methods, and were investigated for their ability to reduce KCl-induced contraction in the isolated rabbit thoracic aorta. All except 2 of the compounds were found to cause a relaxation in the aorta precontracted with KCl to varying degrees. Of the active compounds, 8 analogues caused at least 30% reduction of the control KCl-induced contraction; the most active compound was **16e** which reduced the contraction by 40.6% (30 mM KCl). A representative compound **17i** (which caused 36.3% reduction in the KCl-induced contraction) was tested for hypotensive effects in the anesthesized rat. It was seen that **17i** caused a gradual and sustained reduction in blood pressure. Based on these preliminary results, it would seem that the furoxan-nicorandil derivatives are a useful lead in the design of NO-donor compounds for hypertesion.

Experimental

General Melting points were determined with a capillary apparatus and were uncorrected. The compounds were routinely characterised by IR spectrophotometry (Perkin-Elmer Model 983, KBr tablet). The ^{1}H-NMR spectra were recorded in acetone-d_6, chloroform-d_6/$CDCl_3$ or dimethyl sulfoxide-d_6/DMSO-d_6. Chemical shifts were expressed in δ (ppm) units (JEDL-FX-90Q Fourier transform NMR spectrometer, $Si(Me)_4$/TMS as internal standard). For all final compounds, HR-MS spectra were carried out on a Finnigan FTMS-2000 instrument and were in agreement with the proposed structures. Column chromatography was performed on silica gel (China Qingdao Marine Chemical Company, 100—200 mesh ASTM) with the indicated solvent system. Thin layer chromatography (TLC) was carried out on 5×20 cm plates and 2.5×7.5 cm microscope slides, which were coated with Qingdao Marine silica gel GF_{254} (400 mesh) and 0.8%—1% CMC-Na, activated and dried for 1—2 h at 100—110 °C, then stored in a dryer. Anhydrous magnesium sulphate was used as drying agent for the organic layers. Petroleum ether (30—60 °C) and dicholoromethane were used for chromatography purification and crystallization. Solvent was removed under reduced pressure at room temperature. Intermediates **8**—**10** were synthesised according to methods reported in the literature.[19,20]

***N*-(2-Hydroxyethyl)nicotinic Amide (1)** Concentrated sulphuric acid (5 ml) was added dropwise to a stirred mixture of nicotinic acid (0.2 mol, 25 g) in anhydrous ethanol and cyclohexane (1 : 1, 200 ml). A water separator condensor was attached. The temperature was raised slowly and the mixture was refluxed for 3—6 d with stirring. Removal of the solvent under reduced pressure gave a light-yellow oil which was added to saturated Na_2CO_3 solution with stirring until a pH value of 7 was reached. The mixture was then extracted with ethoxyethane, and the combined organic phase was washed with saturated NaCl, dried with $MgSO_4$ and evaporated. The nicotinic acid ester was obtained as pure colourless oil after vacuum distillation. Then nicotinic acid ester (0.05 mol, 7.2 g) and ethanolamine (5 ml) were added to chloroform with stirring. The mixture was refluxed for 3—4 h, and allowed to stand overnight before the solvent $CHCl_3$, ethanol formed from reaction and the excess of ethanolamine were evaporated under reduced pressure. A white hard solid was obtained, which gave white crystals when recrystallized with acetone. Yield 96%, mp 90—92 °C.

3-Methyl-4-[2(3-pyridineformamido)ethoxycarbonyl]furoxan (11) **1** (0.02 mol, 3.3 g), CH_2Cl_2 (80 ml) and triethylamine (3 ml) were mixed and stirred at a temperature below 30 °C. A light-yellow solution was obtained. A solution of compound (**10**) (0.02 mol) in tetrahydrofuran (THF) was added dropwise at room temperature and a colour change (yellow to black-brown) was observed. The reaction was exothermic and heat was exuded. The mixture was stirred at room temperature for 16 h, after which water was added. The organic phase was washed with water, decolourised with active carbon and filtered. The solution was evaporated to dryness under reduced pressure to give (**11**) as a pure brown solid. Yield 54.5%. mp 112—114 °C. ^{1}H-NMR (DMSO-d_6) δ: 8.98 (d, 1H, pyridine-C_2-H), 8.75—8.66 (s+dd, 2H, pyridine-C_6-H, CONH), 8.23—8.09 (tt, 1H, pyridine-C_4-H), 7.56—7.34 (q, 1H, pyridine-C_5-H), 4.61—4.48 (t, 2H, CH_2OCO), 3.79—3.60 (q, 2H, $NHCH_2$), 2.26 (S, 3H, CH_3). Formula $C_{12}H_{12}N_4O_5$; $(M+H)^+$ Calcd: 293.088047. Found: 293.089550. MS (SCI, *m/z*): 293 (MH^+, base peak), 149 ($C_5H_4NCONHCH_2$–CH_2^+), 121 (C_5H_4N–$CONH^+$). IR (KBr, cm^{-1}): 3250, 3060 (N–H); 1730, 1650 (C=O); 1100 (O=C–O).

***N*-(2-hydroxyethyl)isonicotinic Amide (2)** Concentrated sulphuric acid (1.5 ml) was added dropwise to a stirred mixture of isonicotinic acid (0.1 mol, 13.0 g) in absolute ethanol (30 ml). The mixture was refluxed for 10 d. A hard white solid was formed after the ethanol was evaporated *in vacuo*. The solid dissolved with the addition of saturated Na_2CO_3, and the alkaline solution was then extracted with ethoxyethane. The organic layer was washed with saturated NaCl solution, dried, evaporated and then vacuum distilled, resulting in a pale-yellow oil of ethyl isonicotinate. A mixture of the ethyl isonicotinate (0.02 mol, 3.3 g), ethanolamine (3.0 ml) and chloroform (10 ml) were refluxed for 3—4 h with stirring, after which the solvent chloroform and ethanol were removed *in vacuo*. Ethoxyethane and acetone were then added and a white precipitate was obtained, filtered off, washed with chloroform, acetic ester, acetone, and dried to give the title compound. Yield 96%, mp 130—132 °C.

3-Methyl-4-[2(4-pyridineformamido)ethoxycarbonyl]furoxan (12) A solution of compound (**10**) (0.01 mol) in THF was added dropwise to a stirred mixture of **2** (0.01 mol, 1.6 g) in THF (50 ml) and triethylamine (1 ml) at room temperature. The stirring was continued for 6 h, after which the solvent was evaporated *in vacuo* to give a brown sticky paste, which was poured into water. The solution was filtered to remove some pale brown precipitate. The aqueous solution was extracted with CH_2Cl_2, and the combined organic solution was washed with saturated NaCl, decolorized with 400 mesh silica gel, dried and evaporated to give the title compound as a white solid. It was then purified by washing with ethanol and ethoxythane. Yield 50.5%. mp 168—170 °C. ^{1}H-NMR ($CDCl_3$+DMSO-d_6) δ: 8.85 (s, 1H, CONH), 8.37—8.67 (dd, 2H, pyridine-C_2,C_6-2H), 7.79—7.72 (dd, 2H, pyridine-C_3, C_5-2H), 4.60—4.54 (t, 2H, CH_2OCO), 3.80—3.70 (q, 2H, $NHCH_2$), 2.31 (s, 3H, CH_3). Formula $C_{12}H_{12}N_4O_5$ $(M+H)^+$ Calcd: 293.088047. Found: 293.088075. MS (SCI, *m/z*): 293 (MH^+, base peak), 214 ($CONHCH_2$–CH_2-furoxan), 149 (C_5H_4NCONH–$CH_2CH_2^+$). IR (KBr, cm^{-1}): 3200, 3050 (N–H); 1750, 1650 (C=O); 1100 (O=C–O).

General Method for the Preparation of *N*-Substituted Benzoylpiperazine (7a,b, d—j) Hydrate piperazine (0.006 mol, 0.62 g) and acetic acid (50 ml) were mixed, immediately producing some gaseous fumes and heat was released. The mixture was then stirred until a colourless solution was obtained as it cooled. A solution of the substituted benzoic acid chloride (0.006 mol) in THF (2 ml) obtained by refluxing the relating substituted benzoic acid in thionyl chloride was then added dropwise to the stirred mixture which became turbid. The stirring was continued for about 60 min at room temperature, water was added and the pH was adjusted with NaOH solution to 12. The solution was filtered to remove some white or pale-brown undissolved substances. The aqueous solution was extracted with chloroform, the organic solution was then washed with water or saturated NaCl solution, dried and evaporated *in vacuo* to give the desired compound (**7a**, **b**, **d**—**j**), which was then processed quickly for the next step of the reaction.

General Method for the Preparation of *N*-(3/4-Substituted-benzoyl)-*N'*-[3-methylfuroxanyl-4-carbonyl]piperazine (17a, b, d—j) A solution of compound **10** (0.006 mol) in THF was added dropwise to a stirred mixture of **7a**, **b**, **d**—**j** (0.006 mol) in CH_2Cl_2 (60 ml) and N $(C_2H_5)_3$ (1 ml). Stirring was continued for about 6 h at room temperature, after which the resulting mixture was washed several times with water, 10% HCl and saturated $NaHCO_3$ consecutively. The organic layer was then decolorized with active carbon, dried and evaporated to afford a solid compound which was further purified with acetone or ethanol to give the final compounds (**17a**, **b**, **d**—**j**).

The physical data of the synthesised compounds (**17a, b, d—j**) are given in Table 2. The compounds are *N*-(3-nitrobenzoyl)-*N'*-[3-methyl furoxanyl-4-carbonyl]piperazine (**17a**), *N*-(4-nitrobenzoyl)-*N'*-[3-methyl furoxanyl-4-carbonyl]piperazine (**17b**), *N*-(3-chlorobenzoyl)-*N'*-[3-methyl furoxanyl-4-arbonyl]piperazine (**17d**), *N*-(4-chlorobenzoyl)-*N'*-[3-methyl furoxanyl-4-carbonyl]piperazine (**17e**), *N*-(3-bromobenzoyl)-*N'*-[3-methyl furoxanyl-4-carbonyl]piperazine (**17f**), *N*-(4-bromobenzoyl)-*N'*-[3-methyl furoxanyl-4-carbonyl]piperazine (**17g**), *N*-(3-methoxybenzoyl)-*N'*-[3-methylfuroxanyl-4-carbonyl]piperazine (**17h**), *N*-(4-methoxybenzoyl)-*N'*-[3-methylfuroxanyl-4-carbonyl]piperazine (**17i**), *N*-benzoyl-*N'*-[3-methylfuroxanyl-4-carbonyl]-piperazine (**17j**).

General Method for the Preparation of 3-Methyl-4-[2-(3/4-substituted benzoyl amino) ethylaminocarbonyl]furoxan (15a, b, d—j) Ethylene diamine (0.017 mol, 1.0 g) and acetic acid (50 ml) were slowly mixed together, a large amount of white gas was produced and the reaction was exothermic. A white solid was initially formed but dissolved gradually to form a colourless solution, as it cooled to room temperature. The corresponding benzoic acid chloride derivative (0.01 mol) was then added dropwise with stirring over 30 min at room temperature. After 2 h water was added to the mixture, and the pH adjusted to 12 with NaOH solution. The solution was filtered to remove some white precipitate and the aqueous filtrate was extracted with chloroform, the organic phase was washed with saturated NaCl, dried and evaporated under reduced pressure to afford the intermediate *N*-(2-aminoethyl)-substituted benzoylamide (**5a, b, d—j**) which was used immediately for the next step of the reaction. A solution of compound **10** (0.01 mol) in THF (2 ml) in the presence of triethylamine (0.5 ml) was added dropwise at room temperature to a stirred solution of **5a, b, d—j** in CH_2Cl_2. The stirring was continued 3—6 h and then the reaction mixture was poured into water. The organic layer was washed several times with water, decolorised with active carbon, dried and evaporated under reduced pressure to give the desired derivatives (**15a, b, d—j**) which were recrystallized with ethanol. The physical data of the synthesized compounds (**15a, b, d—j**) are given in Table 2. The compounds are 3-methyl-4-[2-(3-nitrobenzoylamino)-ethylaminocarbonyl]furoxan (**15a**), 3-methyl-4-[2-(4-nitrobenzoylamino)-ethylaminocarbonyl] furoxan (**15b**), 3-methyl-4-[2-(3-chlorobenzoylamino)-ethylaminocarbonyl]furoxan (**15d**), 3-methyl-4-[2-(4-chlorobenzoylamino)-ethylaminocarbonyl]furoxan (**15e**), 3-methyl-4-[2-(3-bromobenzoylamino)-ethylaminocarbonyl]furoxan (**15f**), 3-methyl-4-[2-(4-bromobenzoylamino)-ethylaminocarbonyl]furoxan (**15g**), 3-methyl-4-[2-(3-methoxybenzoylamino)-ethylaminocarbonyl]furoxan (**15h**), 3-methyl-4-[2-(4-methoxybenzoylamino)-ethylaminocarbonyl]furoxan (**15i**), 3-methyl-4-(2-benzoyl aminoethyl aminocarbonyl)furoxan (**15j**).

General Method for the Preparation of 3-Methyl-4-[3(3/4-substituted-benzoyl aminopropyl aminocarbonyl)furoxan (16a, b, d, e, g, i) 1,3-Diaminopropane (0.02 mol, 1.50 g) and acetic acid (50 ml) were reacted together as described for the preparation of 3-methyl-4-[2(3/4-substituted-benzoylamino) ethylaminocarbonyl]furoxan (**15a, b, d—j**). The intermediate *N*-(3-aminopropyl)-substituted-benzoylamide (**6a, b, d, e, g, i**) was first obtained. A mixture of **6** (**a, b, d, e, g, i**) in $CHCl_3$ was similarly reacted with compound **10** (0.02 mol) as described earlier. The physical data of the synthesised compounds (**16a, b, d, e, g, i**) are given in Table 2. The compounds are 3-methyl-4-[3-(3-nitrobenzoylamino)propylaminocarbonyl]furoxan (**16a**), 3-methyl-4-[3-(4-nitrobenzoylamino)propylaminocarbonyl]furoxan (**16b**), 3-methyl-4-[3-(3-chlorobenzoylamino)propylaminocarbonyl]furoxan (**16d**), 3-methyl-4-[3-(4-nitrobenzoylamino)propylaminocarbonyl]furoxan (**16e**), 3-methyl-4-[3-(4-bromobenzoylamino)propylaminocarbonyl]furoxan (**16g**), 3-methyl-4-[3-(4-methoxylbenzoylamino)propylaminocarbonyl]furoxan (**16i**).

General Method for the Preparation of 3-Methyl-4-[2(3/4-substituted-benzoyl amino)ethoxylcarbonyl]furoxan (13a—e, g) Concentrated sulphuric acid (1 ml) was added dropwise to a stirred mixture of the substituted benzoic acid (0.02 mol) in absolute ethanol (100 ml). After refluxing for 8 h, the solution was cooled to room temperature, and cyclohexane (60 ml) was added. The mixture was distilled to evaporate the water formed from the reaction, as well as the solvents cyclohexane and ethanol. A pale-yellow sticky residue was exuded, water was added and the mixture was extracted with ethoxyethane. The organic solution was washed several times with saturated NaCl and water, dried and evaporated *in vacuo* to give the substituted benzoic acid ester. The ester was reacted with ethanolamine (0.02 mol, 1.3 g) in chloroform with stirring. The mixture was then refluxed for 8 h, after which the organic solvents were removed *in vacuo* to give a pale-brown oil which became a sticky solid on cooling in the refrigerator. Subsequent grinding of the sticky solid with some acetone and ethoxyethane gave a white solid which was the intermediate *N*-(2-hydroxyethyl)-substituted-benzoylamides (**3a—e, g**). These intermediates were recrystallized with one of the following solvents: acetone, acetic ester, ethoxyethane, or petroleum ether. A solution of **10** (0.01 mol) in THF (2 ml) was added dropwise to a stirred mixture of **3a—e, g** in dichloromethane (60 ml) in the presence of triethylamine (1 ml). The stirring was continued for 3—6 h, after which the reaction mixture was poured into water. The separated organic solution was washed several times with water, decolorized with active carbon, dried and evaporated under reduced pressure. The expected final derivatives 3-methyl-4-[(2/3-substituted benzoylamino)alkyloxylcarbonyl]furoxan (**13a—e, g**) were obtained after recrystallization with ethanol or ethoxyethane. The physical data of the synthesized compounds (**13a—e, g**) are given in Table 2. The compounds are 3-methyl-4-[2(3-nitrobenzoylamino)ethoxylcarbonyl]furoxan (**13a**), 3-methyl-4-[2(4-nitrobenzoyl amino)ethoxylcarbonyl]furoxan (**13b**), 3-methyl-4-[2(3,4-dinitrobenzoylamino)ethoxylcarbonyl]furoxan (**13c**), 3-methyl-4-[2(3-chlorobenzoylamino)ethoxylcarbonyl]furoxan (**13d**), 3-methyl-4-[2(4-chlorobenzoylamino)ethoxylcarbonyl]furoxan (**13e**), 3-methyl-4-[2(4-bromobenzoylamino)ethoxylcarbonyl]furoxan (**13g**).

General Method for the Preparation of 3-Methyl-4-[3(3/4-substituted-benzoyl-amino)propyloxylcarbonyl]furoxan (14a—c, e) Propanoamine (0.015 mol, 1.03 g) and acetic acid (50 ml) were reacted together as described for the preparation of 3-methyl-4-[2(3/4-substitutedbenzoylamino)-ethoxylcarbonyl]furoxan (**13a—e, g**). The intermediate *N*-(3-hydroxypropyl)-3/4-substituted-benzoylamide (**4a—c, e**) were first obtained. A mixture of **4a—c,e** in CH_2Cl_2 was similarly reacted with compound **10** (0.01 mol) as described earlier. The physical data of the synthesised compounds (**14a—c, e**) are given in Table 2. The compounds are 3-methyl-4-[3(3-nitrobenzoylamino)propyloxylcarbonyl]furoxan (**14a**), 3-methyl-4-[3(4-nitrobenzoylamino)propyloxylcarbonyl]furoxan (**14b**), 3-methyl-4-[3(3,4-dinitrobenzoylamino)propyloxylcarbonyl]furoxan (**14c**), 3-methyl-4-[3(4-chlorobenzoylamino)propyloxylcarbonyl]furoxan (**14e**).

Pharmacology. Experiments on Denuded Thoracic Aorta Isolated from Rabbits The thoracic aorta was isolated from male or female rabbits weighting 1.8—2.5 kg, which were sacrificed by a sharp blow on the head. Helicoid strips were prepared according to known methods and mounted in an organ bath containing Krebs–Henseleit buffer solution pH 7.4 of the following composition: NaCl, 120; KCl, 4.8; $CaCl_2$, 2.5; $MgSO_4 \cdot 7H_2O$, 1.4; KH_2PO_4, 1.2; $NaHCO_3$, 25; glucose 11 mmol/l; Na_2EDTA 13.4 μmol/l. The tissue was maintained at 37 °C and aerated with 95% O_2—5% CO_2. After an equilibrium period of 2 h, the aortic strips were contracted by addition of either 30 or 80 mM KCl solution. The sample (10 μM) was then added and its effect on KCl-induced contraction was monitored. Each experiment was repeated 3 times. The drug was dissolved in DMSO–saline, and the volume ratio of DMSO did not exceed 0.5% of the bath volume. The effect of the drug on the aorta precontracted with KCl was expressed as an inhibitory ratio which is given as Eq. 1.

$$\%\ \text{inhibition of KCl-induced contraction} = \frac{\left(\begin{matrix}\text{height of control}\\ \text{KCl contraction}\end{matrix}\right) - \left(\begin{matrix}\text{height of KCl contraction}\\ \text{in presence of drug}\end{matrix}\right)}{\text{height of control KCl contraction}} \quad (1)$$

Effect of Blood Pressure in Anaesthesised Rats Male or female rats weighting about 250 g were anesthesised and carefully dissected to expose the carotid artery. The artery was cannulated and a pressure transducer connected to a Grass Polygraph recorder was attached. The systolic, diastolic and mean arterial (MAP) pressures were monitored until steady values were obtained. The drug was administered *via* intravenous injection at a dose of 1.5 mg/kg and the pressures were monitored over a period of 6 h.

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