Cardioselective Antiischemic ATP-Sensitive Potassium Channel Openers. 2. Structure–Activity Studies on Benzopyranylcyanoguanidines: Modification of the Benzopyran Ring

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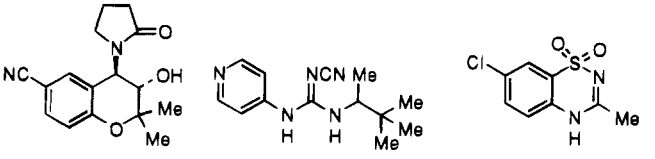
Received January 17, 1995[⊗]

The ATP-sensitive potassium channel (K_{ATP}) openers are of considerable interest as myocardial protecting agents. However, there exists a narrow window of safety for the use of first-generation compounds as antiischemic agents due to their powerful peripheral vasodilating effects, which can result in underperfusion of the area already at risk. We have recently disclosed the discovery of benzopyranylcyanoguanidine type K_{ATP} openers (BMS-180448) which are more selective for the ischemic myocardium compared to the first-generation compounds. This publication deals with structure–activity relationships for the antiischemic activity of the lead compound **8**. The presence of an electron-withdrawing group at C6, an sp^3 center at C4, and a *gem*-dimethyl group at C2 appears to be essential for antiischemic activity. Cyanoguanidine can be replaced with a urea moiety. The results reported here support the hypothesis that distinct structure–activity relationships exist for antiischemic and vasorelaxant activities of compounds related to **8** and cromakalim. The trifluoromethyl analog **10** is 550-fold more selective *in vitro* for the ischemic myocardium compared to the first-generation agent cromakalim. The reasons for the selectivity of these compounds for the ischemic myocardium are not clear at the present time. They may be related to the existence of receptor subtypes in smooth muscle and the myocardium.

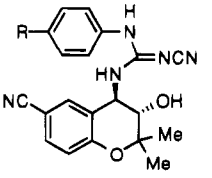
Introduction

We and others have shown that ATP-sensitive potassium channel (K_{ATP}) openers have direct cardioprotective properties independent of their vasodilator actions.[1] Being potent peripheral vasodilators, the use of first-generation compounds (**1-6**) for the treatment of acute myocardial ischemia is limited due to the possibility of hemodynamic alterations with systemic administration. Therefore, cardioselective agents are required to exploit the full potential of K_{ATP} openers for the treatment of myocardial ischemia. The need for cardioselective K_{ATP} openers is further highlighted by the potential involvement of K_{ATP} opening in myocardial preconditioning, wherein short episodes of ischemia can protect the heart from a subsequent long period of ischemia.[2] Although the mechanism of preconditioning is still debatable, evidence is accumulating that the K_{ATP} opening may be involved in mediating the cardioprotective actions associated with preconditioning in animal models[3] and humans.[4] Therefore, K_{ATP} may be an integral part of the heart's endogenous protective mechanism to minimize injury following ischemic insult. K_{ATP} openers have been hypothesized to be "chemical preconditioning agents".[5]

In a recent communication, we reported the discovery of BMS-180448 (**7**) which is 200-fold more selective for the ischemic myocardium than the reference agent cromakalim (**1**).[6] This paper describes our preliminary structure–activity studies on the lead compound **8** with emphasis on the benzopyran ring. We demonstrate that no correlation exists between antiischemic and vasorelaxant potencies for a series of compounds related to **8** and the reference agent cromakalim (**1**). We speculate



that the antiischemic and vasorelaxant effects of K_{ATP} openers are mediated via different receptor subtypes.



7 R = Cl (Chiral)
8 R = H (Racemic)

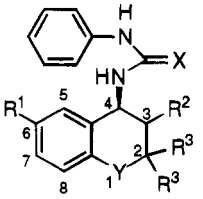
Results and Discussion

The vasorelaxant potencies were determined by measurement of IC_{50} values for relaxation of the methoxamine-contracted rat aorta, as described previously.[7] Most vasorelaxing agents were able to inhibit 70–100% of the maximum contraction induced by methoxamine. The antiischemic potencies *in vitro* were determined by measurement of EC_{25} values for increase in time to the onset of contracture in globally ischemic isolated rat hearts.[8] Time to contracture is defined as the time

[⊗] Abstract published in *Advance ACS Abstracts*, May 15, 1995.

0022-2623/95/1838-1966$09.00/0

Table 1. Vasorelaxant and Antiischemic Potencies of Benzopyranylcyanoguanidine/urea Analogs **8**–**31** and Cromakalim (**1**)



compd	R^1	R^2	R^3	X	Y	time to contracture[a] EC_{25}, μM, or % inc. at 10 μM	vasorelaxant potencies[b] IC_{50}, μM (95% CI)	ratio EC_{25}/IC_{50}
8	CN	*trans*-OH	Me	NCN	O	11.0	1.4 (0.98, 1.93)	7.9
9	CN	*trans*-OH	Me	O	O	5.1	0.8 (0.51, 1.28)	6.4
10	CF_3	*trans*-OH	Me	NCN	O	10.0	19.2 (13.0, 28.4)	0.5
11	CF_3	*trans*-OH	Me	O	O	2.7	1.1 (0.78, 1.59)	2.5
12	$COCH_3$	*trans*-OH	Me	NCN	O	8.5	4.0 (2.0, 8.1)	2.1
13	$COCH_3$	*trans*-OH	Me	O	O	4.5	1.2 (0.93, 1.6)	3.8
14	NH_2	*trans*-OH	Me	NCN	O	0%	59.6 (27.6, 129.0)	
15	6,7-oxadiazole	*trans*-OH	Me	NCN	O	6%	8.8 (6.15, 12.5)	
16	6,7-oxadiazole	*trans*-OH	Me	O	O	13.0	1.4 (1.0, 1.95)	9.3
17	CN	*cis*-OH	Me	NCN	O	9%	17.0 (13.6, 21.2)	
18	CN	*cis*-OH	Me	O	O	102.6	6.2 (3.96, 9.76)	16.5
19	CN	3,4-olefin	Me	NCN	O	0%	6.9 (4.46, 10.7)	
20	CN	3,4-olefin	Me	O	O	7%	17 (13.5, 21.4)	
21	CN	*trans*-OAc	Me	NCN	O	6.0	2.6 (1.62, 4.09)	2.3
22	CN	*trans*-OAc	Me	O	O	3%	4.4 (2.44, 7.77)	
23	CN	H	Me	NCN	O	0%	14.0 (10.5, 18.7)	
24	CN	H	Me	O	O	5.3	1.8 (1.42, 2.25)	2.9
25	CN	*trans*-OH	H	NCN	O	0%	194 (136, 278)	
26	CN	*trans*-OH	H	O	O	6%	98.1 (33.3, 289.0)	
27	CN	*trans*-OH	Me	NCN	NH	0%	92.8 (64.4, 133.0)	
28	NO_2	*trans*-OH	Me	NCN	single bond	10.7	0.57 (0.36, 0.9)	18.8
29	NO_2	*trans*-OH	Me	O	single bond	6.5	0.18 (0.12, 0.27)	36.1
30	CN	H	Me	NCN	single bond	22.0	2.6 (1.1, 5.9)	8.5
31	CN	H	Me	O	single bond	9.4	1.3 (0.67, 2.42)	7.2
1, cromakalim						8.9	0.032 (0.021, 0.049)	278.1[c]

[a] Antiischemic potency was determined by measurement of EC_{25}, concentration necessary for increase in time to contracture by 25%, in the globally ischemic rat hearts. Time to contracture was defined as the time necessary during total global ischemia to increase end diastolic pressure by 5 mmHg. Each value is an average of three determinations and within ±20% (approximately). [b] Vasorelaxant potency was assessed by measurement of IC_{50} for inhibition of methoxamine-contracted rat aorta. IC_{50} is presented as a mean with 95% confidence interval in parentheses, $n = 4$ or higher. [c] Data presented previously in ref 6.

necessary during total global ischemia to increase end diastolic pressure by 5 mmHg.[8] As contracture develops, the heart becomes less compliant due to rigor bond formation ("stone heart"), presumably caused by loss of ATP. The ratio of EC_{25} value for time to contracture and IC_{50} value for vasorelaxant potency indicates selectivity *in vitro* for the ischemic myocardium. Since the two tests are quite different from each other, the ratio of potencies does not predict absolute selectivity *in vivo*. It only serves as a guiding principle to select compounds for *in vivo* testing. We have previously validated these *in vitro* tests by detailed *in vivo* studies on BMS-180448 (**7**).[9] BMS-180448 shows antiischemic efficacy in animal models of myocardial iscemia without effect on peripheral hemodynamic variables. All compounds reported in this publication are racemic mixtures for comparison with the lead compound **8**.

Since our earlier studies indicated that cyanoguanidine (**8**) and urea (**9**) analogs have similar antiischemic potencies,[1] we evaluated both series of compounds (Table 1). With the exception of cyanoguanidine analog **21** which is more potent than its urea counterpart **22**, urea analogs in general are slightly more potent than the corresponding cyanoguanidines (**8** vs **9**, **10** vs **11**, **12** vs **13**, **15** vs **16**, **23** vs **24**, **28** vs **29**, **30** vs **31**). Although more potent as antiischemic agents, the urea analogs are also more potent than cyanoguanidines as vasorelaxant agents, offering no advantage over cyanoguanidines. Our earlier studies indicated that an electron withdrawing group at C6 of benzopyran is required for antiischemic activity.[1] That requirement was further confirmed by the preparation of trifluoromethyl (**10**, **11**) and acetyl (**12**, **13**) analogs of the lead compound **8**. Lack of antiischemic potency in the amino analog **14** also supports the conclusion that optimum antiischemic potency is achieved with an electron-withdrawing group at C6 of the benzopyran ring. The disubstituted analogs **15** and **16** offer no improvement in antiischemic potency over the monosubstituted derivatives **8**–**13**.

As shown by the comparison of **8**/**9** with **17**/**18**, inversion of the C3-hydroxyl leads to a large drop in antiischemic potency. Lack of antiischemic activity in the dehydration products (**19** and **20**) of **8** and **9**, respectively, indicates that an sp^3 carbon is preferred at C4 of benzopyran. Acetylation (**21**, **22**) of the hydroxyl group (**8**, **9**) has a variable effect on biological activity, as does its deletion (**23**, **24**). These results indicate that the effects of C3 and C4 moieties are interdependent. The *gem*-dimethyl group appears to be mandatory as the desmethyl analogs **25** and **26** are devoid of antiischemic activity. While replacement of the oxygen of benzopyran (**8**) with an amino group (**27**) is detrimental to antiischemic and vasorelaxant potencies, its removal (**28**, **29**) maintains antiischemic potency, though in **28** and **29** the cyano group has been replaced with the nitro group. Previous studies have shown that changing the cyano to a nitro group at C6

Table 2. Physical Properties of Cyanoguanidine/Urea Analogs **8–31**

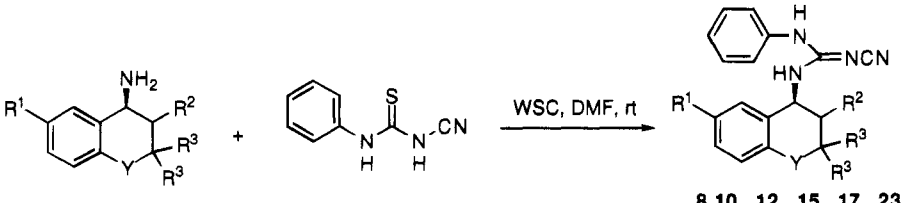
compd	mol formula	microanal.	physical char	mp, °C (crystn solvt)[a]
8	see ref 6			
9	see ref 6			
10	$C_{20}H_{19}F_3N_4O_2$	C, H, N, F	colorless solid	182–3 (A)
11	$C_{19}H_{19}F_3N_2O_3$	C, H, N, F	colorless solid	174–5 (A)
12	$C_{21}H_{22}N_4O_3 \cdot 0.57H_2O$	C, H, N	colorless solid	182–4 (B)
13	$C_{20}H_{22}N_2O_4 \cdot 0.44H_2O$	C, H, N	colorless solid	210–1
14	$C_{19}H_{21}N_5O_2 \cdot 0.39H_2O$	C, H, N	off-white solid	235–7 (C)
15	$C_{19}H_{18}N_6O_3 \cdot 0.35H_2O$	C, H, N	off-white solid	219–20
16	$C_{18}H_{18}N_4O_4$	C, H, N	off-white solid	215–6
17	$C_{20}H_{19}N_5O_2$	C, H, N	colorless solid	122–4 (C)
18	$C_{19}H_{19}N_3O_3$	C, H, N	colorless solid	226–227
19	$C_{20}H_{17}N_5O \cdot 0.39H_2O$	C, H, N	colorless solid	247–8 (D)
20	$C_{19}H_{17}N_3O_2 \cdot 0.2H_2O$	C, H, N	colorless solid	310–4 dec (E)
21	$C_{22}H_{21}N_5O_3$	C, H, N	colorless solid	239–40 (F)
22	$C_{21}H_{21}N_3O_4$	C, H, N	colorless solid	263–4 (?)
23	$C_{20}H_{19}N_5O \cdot 0.2H_2O$	C, H, N	colorless solid	223–5 (F)
24	$C_{19}H_{19}N_3O_2$	C, H, N	colorless solid	214–5 (?)
25	$C_{18}H_{15}N_5O_2 \cdot 0.26H_2O$	C, H, N	colorless solid	219–20 (C)
26	$C_{17}H_{15}N_3O_3$	C, H, N	colorless solid	239–40
27	$C_{20}H_{20}N_6O \cdot 0.4H_2O$	C, H, N	colorless solid	218–9 (B)
28	$C_{19}H_{19}N_5O_3$	C, H, N	off-white solid	249–51 (G)
29	$C_{18}H_{19}N_3O_4$	C, H, N	colorless solid	194–5 (B)
30	$C_{20}H_{19}N_5 \cdot 0.22H_2O$	C, H, N	colorless solid	215–7
31	$C_{17}H_{15}N_3O_3$	C, H, N	colorless solid	239–40

[a] A, isopropyl ether–hexanes; B, ethyl acetate; C, isopropyl ether; D, dichloromethane–methanol; E, methanol; F, ethanol; G, methanol–isopropyl alcohol.

of the benzopyran has no effect on antiischemic potency.[6] The deshydroxyindane analogs **30** and **31** maintain significant antiischemic potency. These results suggest that the oxygen atom of the benzopyran ring is not mandatory for antiischemic or vasorelaxing activities.

The selectivity ratio, an estimate of cardiac selectivity *in vitro*, varies 550-fold, being 0.5 for compound **10** and 278 for the reference agent cromakalim (**1**) (Table 1). Clearly, there is no correlation between antiischemic and vasorelaxant potencies. These results support the hypothesis that distinct structure–activity relationships exist for antiischemic and vasorelaxant potencies of K_{ATP} openers. The molecular basis for this difference in structure–activity relationships is not clear at the present time. These pharmacological effects are mediated either by different mechanisms or via receptor subtypes. Because the cardioprotective and vasorelaxant effects of analogs of **8** and cromakalim are inhibited by K_{ATP} blockers (e.g., glyburide),[6,10] it is likely that K_{ATP} opening is still involved in their mechanism of action. We speculate the existence of receptor subtypes in smooth muscle and the cardiac tissue. The other possible explanation for the distinction between structure–activity relationships for vasorelaxant and antiischemic activities of K_{ATP} openers may be related to the differences in the regulation of K_{ATP} in various tissues. Mediators such as arachidonic acid metabolites,[11] fatty acids,[12] lactate,[13] adenosine,[14] and intracellular acidification[15] can affect the activity of metabolically regulated K_{ATP}. Agents that affect the intracellular concentrations of these mediators can be principle affect this channel. Regardless of the explanation, results reported in this paper support that it is possible to find antiischemic K_{ATP} openers with a lower degree of vasorelaxant potency compared to the first-generation agents (**1**–**6**). Further, we have shown that such agents (e.g., BMS-180448) can protect the ischemic myocardium without hemodynamic changes,[9,16] thus validating the selectivity data *in vitro*. These types of cardiac

Scheme 1[a]



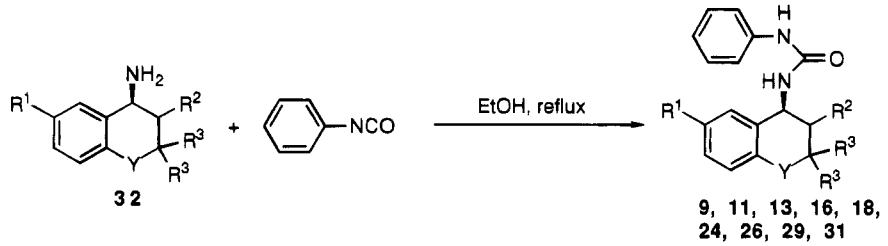
32a (8,9)[a]
32b (10,11)
32c (12,13)
32d (15,16)
32e (17,18)
32f (23,24)
32g (25,26)
32h (27)
32i (28, 29)
32j (30, 31)

33

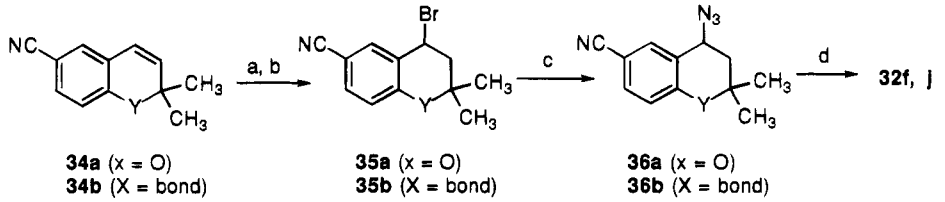
8,10, 12, 15, 17, 23, 25, 27, 28, 30

[a] Numbers in parentheses correspond to the products prepared from **32**; for R^1–R^3, X, and Y, see Table 1.

Scheme 2

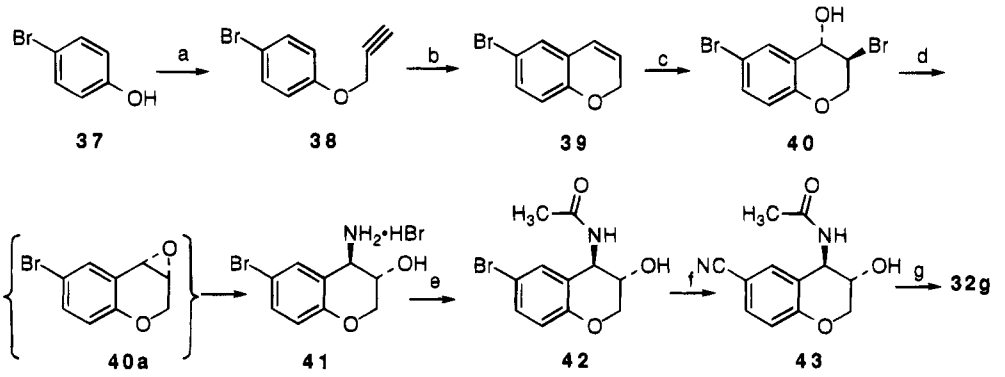


Scheme 3[a]



[a] Reagents: (a) hydrogen, 10% Pd/C, ethanol; (b) *N*-bromosuccinimide, AIBN, carbon tetrachloride, 75% from **34a**; (c) sodium azide, DMF, rt, 78%; (d) H_2, 10% Pd/C, ethanol, 87%.

Scheme 4[a]



[a] Reagents: (a) propargyl chloride, potassium carbonate, acetone, 96%; (b) *N,N*-diethylaniline, Δ, 46%; (c) *N*-bromosuccinimide, DMSO–H_2O, 81%; (d) NH_4OH, EtOH, THF, 97%; (e) acetyl chloride, potassium carbonate, THF, H_2O, 87%; (f) CuCN, *N*-methylpyrrolidone, heat, 58%; (g) sulfuric acid, dioxane, water, heat, 72%.

selective agents are expected to have a higher window of safety for the treatment of acute myocardial ischemia.

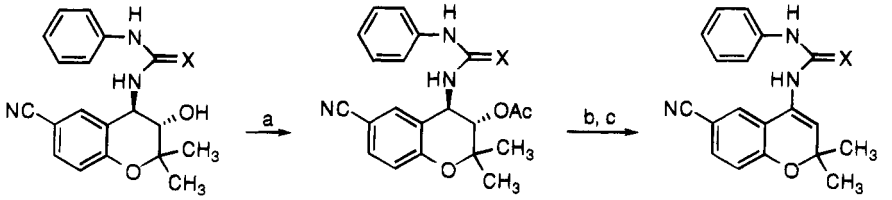
Chemistry. The cyanoguanidine analogs **8**, **10**, **12**, **15**, **17**, **23**, **25**, **27**, **28**, and **30** were prepared by treatment of the amines **32** with *N*-cyano-*N*-phenylthiourea (**33**) in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (water soluble carbodiimide, WSC) in dimethylformamide (Scheme 1). The details of this method are described.[17] The corresponding urea analogs **9**, **11**, **13**, **16**, **18**, **24**, **26**, **29**, and **31** were obtained in excellent yields by simple treatment of the amines **32** with phenyl isocyanate in ethanol (Scheme 2).[18] Most of the benzopyranylamines (**32a-e,h,i**) employed in these reactions were prepared by the literature methods.[19]

The amine (**32f**) for the protio analogs **23** and **24** was prepared from the olefin **34a**[20] by a four-step sequence. Hydrogenation of the olefin **34a** followed by radical bromination (*N*-bromosuccinimide, AIBN) of the crude product gave bromide **35a** in 75% overall yield. Treatment of bromide **35a** with sodium azide and reduction of the resulting azide **36a** by catalytic hydrogenation (Scheme 3) provided the desired amine **32f**. The same sequence of steps can be applied for the synthesis of deshydroxyindanylamine **32j** from **34b**.[19d]

The synthesis of amine **32g** for the preparation of desmethyl analogs **25** and **26** is summarized in Scheme 4. The alkylation of 4-bromophenol (**37**) with propargyl chloride followed by thermal rearrangement of **38** provided the chromene **39** in approximately 45% overall yield from **37**. Direct epoxidation of **39** turned out to be problematic. Therefore, bromohydrin **40** was prepared by treatment of **39** with aqueous *N*-bromosuccinimide. Ammonolysis of bromohydrin **40** gave the *trans*-amino alcohol **41**, presumably via the epoxide intermediate **40a**. The amino group in **41** was acetylated (**42**), and the bromine was replaced with the cyano group (**43**) by heating with copper cyanide in *N*-methylpyrrolidone. The acetate was removed by heating **43** with sulfuric acid in dioxane to provide the desired product (**32g**) in 72% yield. It is to be pointed out that the use of 4-bromophenol, rather than the obvious 4-cyanophenol, in this sequence was necessitated due to the failure of the cyano intermediate (corresponding to **38**) to undergo rearrangement (**38** → **39**).

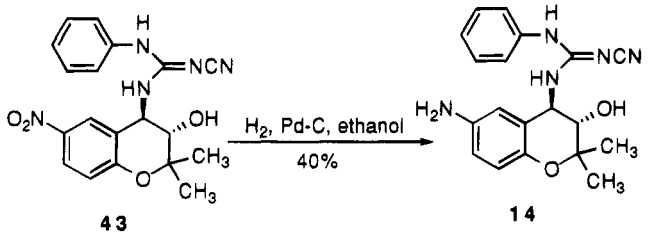
Acetylation of **8** and **9** to **21** and **22**, respectively, was carried out in a straightforward manner (pyridine/acetic anhydride) (Scheme 5). Elimination of the C3-acetate of **21** and **22** under basic conditions (DBU) provided the olefinic analogs **19** and **20**, respectively (Scheme 5). Direct reduction of the olefin in **19/20** to **23/24** gave a mixture of products. Consequently, the protio analogs **23** and **24** were prepared from the deshydroxy amine **32f** by the standard coupling reaction with thiourea. The

Scheme 5[a]



[a] Reagents: (a) acetic anhydride, pyridine, rt, 79% (**21**), 92% (22); (b) 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), toluene, rt, 64% (**19**); (c) DBU, DMF, 100 °C, 36% (**20**).

Scheme 6



amino analog **14** was obtained by hydrogenation of the corresponding nitro compound **44**[1] using palladium on charcoal catalyst (Scheme 6).

Conclusion

The results presented here demonstrate that distinct structure–activity relationships exist for antiischemic and vasorelaxant activities for a series of analogs related to the lead compound **8** and cromakalim. Urea analogs are slightly more potent than the corresponding cyanoguanidines. Depending on the identity of the C4-substituent, the requirements around the pyran ring are variable. The presence of *gem*-dimethyl groups at C2 and an sp^3 carbon at C4 are essential for antiischemic potency. The trifluoromethyl cyanoguanidine **10** is 550-fold more selective *in vitro* for the ischemic myocardium compared to cromakalim (**1**). These data are consistent with the working hypothesis that the structural requirements for antiischemic and vasorelaxant activities are quite distinct. The reasons for this difference in structure–activity relationships for the two activities are not known at the present time. We speculate on the existence of receptor subtypes in smooth muscle and the cardiac tissue Identification of binding protein(s) for K_{ATP} openers in the two tissues is required to explain these findings at the molecular level.

Experimental Section

Chemistry. Typical Procedure for the Synthesis of Cyanoguanidines Illustrated by the Preparation of *trans*-*N*″-Cyano-*N*-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)-*N*′-phenylguanidine (8). The solution of *N*-cyano-*N*′-phenylthiourea, sodium salt (1.06 g, 5.96 mmol, prepared by the treatment of phenyl isothiocyanate with monosodium cyanamide[17]) and *trans*-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (1.0 g, 4.59 mmol) in dimethylformamide (5 mL) under argon was treated with 1-[3-(dimethylamino)propyl]-2-ethylcarbodiimide hydrochloride (1.17 g, 5.96 mmol). The reaction mixture was stirred at room temperature for 2 h and partitioned between 5% citric acid and ethyl acetate. The aqueous phase was reextracted with ethyl acetate, and the combined extracts were washed with water, sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the colorless residue was triturated with ether to yield *trans*-*N*″-cyano-*N*-(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)-*N*′-phenylguanidine (**8**) (1.03 g, 62.4%): ^{1}H NMR (DMSO-d_6) δ 9.28 (s, 1H), 7.58 (m, 3H), 7.35 (m, 4H), 7.15 (m, 1H), 6.90 (d, J = 8.4 Hz, 1H), 5.92 (br s, 1H), 4.92 (t, J = 9.0 Hz, 1H), 3.72 (br d, J = 5.2 Hz, 1H), 1.41, 1.18 (s, 3 H each); ^{13}C NMR (DMSO-d_6) δ 159.2, 156.3, 137.2, 132.6, 132.5, 129.0, 124.7, 123.6, 119.1, 117.8, 117.0, 102.6, 80.4, 70.9, 51.9, 26.6, 18.6; IR (KBr) 2250, 2185, 1609, 1489 cm^{-1}.

Typical Procedure for the Synthesis of Urea Analogs Illustrated by the Preparation of *trans*-*N*-[3,4-Dihydro-3-hydroxy-2,2-dimethyl-6-(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-*N*′-phenylurea (11). A suspension of *trans*-4-amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(trifluoromethyl)-2*H*-1-benzopyran (0.5 g, 1.9 mmol) in ethanol (5 mL) under argon was treated with phenyl isocyanate (0.23 g, 1.9 mmol), and the reaction mixture was heated at reflux temperature for 4 h. The product precipitated out of the reaction mixture. The reaction mixture was then concentrated *in vacuo*, and the residue was triturated with isopropyl ether–hexanes to give *trans*-*N*-[3,4-dihydro-3-hydroxy-2,2-dimethyl-6-(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-*N*′-phenylurea as a colorless solid (0.5 g, 68.6%): ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 1H), 7.32 (d, J = 9.8 Hz, 1H), 7.17 (m, 5H), 7.0 (m, 1H), 6.77 (d, J = 8.2 Hz, 1H), 5.22 (br d, 1H), 4.80 (br t, 1H), 3.45 (d, J = 9.4 Hz, 1H), 1.37 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.0, 156.5, 139.1, 137.3, 129.4, 126.5, 125.0, 124.7, 122.0, 121.7, 118.0, 79.6, 76.4, 51.4, 26.3, 18.2; IR (KBr) 1500.9, 1558.3, 1598.8, 1647.8, 2981.4, 3391.3 cm^{-1}.

4-Amino-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (32f). A. 3,4-Dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile. A solution of 6-cyano-2,2-dimethyl-2*H*-1-benzopyran (**34a**)[20] (5.5 g, 29.7 mmol) in anhydrous ethanol (40 mL) was hydrogenated at atmospheric pressure using 10% palladium on charcoal catalyst (0.35 g). The catalyst was filtered off using a Celite pad and the filter cake washed with ethyl acetate. The filtrate was concentrated under vacuum to obtain a yellow oil (5.71 g). The crude product was dissolved in ethyl acetate (60 mL), washed successively with 5% hydrochloric acid, saturated sodium bicarbonate solution, and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to yield the title compound (5.14 g, 92.4%) as a yellow solid (mp 30–31 °C) which was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.37 (s, 1H), 7.34 (s, 1H), 6.80 (d, J = 8.8 Hz, 1H), 2.78 (t, J = 6.7 Hz, 2H), 1.80 (t, J = 6.7 Hz, 2H), 1.35 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 157.95, 133.82, 131.34, 122.07, 119.53, 118.24, 102.66, 75.76, 32.13, 26.81, 22.06.

B. 4-Bromo-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (35a). To a solution of 3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (6.40 g, 34.18 mmol) in carbon tetrachloride (90 mL) was added *N*-bromosuccinimide (6.69 g, 37.6 mmol). The solution was purged with argon. A solution of 2,2′-azobis(2-methylpropionitrile) (0.4 g, 3.42 mmol) in carbon tetrachloride (10 mL) was added; the reaction mixture was heated at reflux for 30 min while being irradiated with high-intensity visible light. The reaction mixture was concentrated under vacuum, and the residue was dissolved in ethyl acetate (75 mL). The solution was washed successively with water (4 × 75 mL), saturated sodium bicarbonate, and brine and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to obtain an orange

semisolid which was triturated with cold pentane to provide an off-white solid (7.19 g). This was crystallized from ethyl acetate–hexanes (10:90) to yield the title compound (4.60 g) as off-white needles, mp 94–95 °C. The mother liquors were combined and chromatographed on silica gel eluting with hexane–ethyl acetate (19:1) to afford additional product (2.26 g) for a combined yield of 75.4%: ^{1}H NMR ($CDCl_3$) δ 7.86 (d, J = 1.2 Hz, 1H), 7.42 (dd, J = 1.8 and 8.8 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 5.35 (d, J = 7.6 Hz, 1H), 2.45 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.71, 136.25, 133.21, 122.61, 118.87, 103.81, 76.54, 43.57, 40.34, 28.36, 25.45.

C. 4-Azido-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (36a). A solution of 4-bromo-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (**35a**) (6.73 g, 25.29 mmol) in dry DMF (100 mL) was treated with sodium azide (3.79 g, 50.57 mmol) and stirred at room temperature under argon for 4 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed successively with water and brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under vacuum and the residue triturated with pentane to provide the title compound (4.50 g, 78%) as an off-white solid, mp 63–64 °C: ^{1}H NMR ($CDCl_3$) δ 7.69 (s, 1H), 7.46 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 4.59 (dd, J = 6.5 and 2.3 Hz, 1H), 2.24 (m, 1H), 2.01 (m, 1H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.66, 133.79, 133.41, 121.20, 119.24, 104.21, 76.80, 53.73, 38.30, 28.97, 26.29.

D. 4-Amino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (32f). A solution of 4-azido-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (**36a**) (2.00 g, 8.77 mmol) in absolute ethanol (50 mL) was hydrogenated at atmospheric pressure using 10% palladium on charcoal catalyst (0.25 g). The reaction mixture was filtered, and the filtrate was acidified to pH 1–2 with concentrated HCl (0.85 mL) and concentrated under vacuum to a white solid. The residue was dissolved in water and extracted with ethyl acetate. The aqueous layer was adjusted to pH 11–12 with 50% NaOH solution and extracted with ethyl acetate. The extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to provide the title compound (1.54 g, 87%) as a yellow oil which solidified upon standing. The product was used for the next step without further purification: ^{1}H NMR (DMSO-d_6) δ 8.01 (s, 1H), 7.51 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 3.86 (d, J = 5.9 Hz, 1H), 2.07 (dd, J = 5.9 and 13.5 Hz, 1H), 1.56 (m, 1H), 1.39 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 156.82, 132.51, 131.59, 129.40, 119.47, 117.45, 101.70, 76.99, 43.13, 42.47, 29.39, 24.70.

The synthesis of **32j** from **34b**[19d] can be carried out in an analogous manner.

***trans*-4-Amino-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran-6-carbonitrile (32g). A. 1-Bromo-4-(2-propynyloxy)benzene (38).** A mixture of 4-bromophenol (**37**) (17.4 g, 0.1 mol), propargyl chloride (8.20 g, 0.11 mol), potassium carbonate (13.8 g, 0.1 mol), and potassium iodide (1.66 g, 0.01 mol) in acetone (250 mL) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature, the solid filtered off, and the filtrate evaporated. The residue was partitioned between ethyl acetate and water. The organic phase was washed with 2 N NaOH and brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to obtain an orange oil (20.2 g, 96%). The product was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 4.66 (s, 2H), 2.52 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 156.51, 132.23, 116.68, 113.80, 78.06, 75.85, 55.89.

B. 6-Bromo-2*H*-1-benzopyran (39). A solution of 1-bromo-4-(2-propynyloxy)benzene (**38**) (10.0 g, 47.4 mmol) in *N*,*N*-diethylaniline (50 mL) was heated at reflux for 12 h. The diethylaniline was removed under vacuum (65 °C at 10 mmHg), and the residue was chromatographed on silica gel eluting with 5% methylene chloride in hexanes to obtain the desired product (4.63 g, 56.3%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.06 (dd, J = 2.4 and 8.2 Hz, 1H), 6.94 (s, 1H), 6.53 (d, J = 8.8 Hz, 1H), 6.21 (d, J = 10.0 Hz, 1H), 5.67 (m, 1H), 4.70 (d, J = 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 152.97, 131.45, 128.89, 124.00, 123.39, 123.10, 117.34, 113.11, 65.51.

C. *trans*-3,6-Dibromo-3,4-dihydro-2*H*-1-benzopyran-4-ol (40). To an ice cold solution of 6-bromo-2*H*-1-benzopyran (**39**) (3.0 g, 14.2 mmol) in 4:1 dimethyl sulfoxide/water (20 mL) was added *N*-bromosuccinimide (2.53 g, 14.2 mmol). The reaction mixture was stirred at 0 °C for 1 h and partitioned between water and ethyl acetate. The organic fraction was separated, washed with water and brine, and dried over $MgSO_4$, and the solvent was evaporated to obtain an off-white solid (4.3 g). The crude product was crystallized from hexane–ether to provide the title compound (3.54 g, 81%) as a white solid, mp 120–121 °C: ^{1}H NMR ($CDCl_3$) δ 7.50 (d, J = 2.4 Hz, 1H), 7.34 (dd, J = 2.4 and 8.8 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 4.84 (s, 1H), 4.48 (d, J = 8.8 Hz, 1H), 4.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 152.25, 132.99, 131.80, 123.18, 118.71, 113.43, 69.53, 66.36, 47.44.

D. *trans*-4-Amino-6-bromo-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran Hydrobromide (41). A solution of *trans*-3,6-dibromo-3,4-dihydro-2*H*-1-benzopyran-4-ol (**40**) (3.86 g, 12.5 mmol) in tetrahydrofuran (20 mL), ethanol (20 mL), and 30% ammonium hydroxide (20 mL) was stirred in a stoppered bottle for 48 h. The volatiles were removed under vacuum, and the crude product was triturated with isopropyl ether to provide the title compound (3.95 g, 97%) as a colorless solid, mp 235–240 °C dec: ^{1}H NMR (CD_3OD) δ 7.60 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 2.4 and 8.8 Hz, 1H), 6.80 (d, J = 8.8 Hz, 1H), 4.26 (dd, J = 1.5 and 10.2 Hz, 1H), 4.11 (m, 3H); ^{13}C NMR (CD_3OD) δ 154.68, 133.66, 132.83, 122.92, 120.01, 113.85, 67.86, 66.85, 52.48.

E. *trans*-*N*-(6-Bromo-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran-4-yl)acetamide (42). To a slurry of *trans*-4-amino-6-bromo-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran hydrobromide (**41**) (5.49 g, 16.9 mmol) in tetrahydrofuran (40 mL) and 20% sodium carbonate solution (10 mL) at room temperature was added excess acetyl chloride while maintaining the reaction pH >9 with a simultaneous addition of 20% aqueous sodium carbonate solution. The reaction mixture was stirred for 30 min at room temperature and partitioned between ethyl acetate and water. The organic phase was washed with 5% hydrochloric acid solution, saturated sodium bicarbonate solution, and brine and dried over anhydrous $MgSO_4$. The solvent was removed, and the residue was triturated with isopropyl ether to afford the title compound (4.22 g, 87.3%) as a colorless solid, mp 213–214 °C: ^{1}H NMR (DMSO-d_6) δ 8.29 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 2.4 and 8.8 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 5.43 (d, J = 4.1 Hz, 1H), 4.71 (m, 2H), 3.76 (m, 1H), 1.87 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.29, 153.65, 132.77, 131.45, 124.74, 118.75, 111.78, 67.12, 65.10, 48.97, 22.97.

F. *trans*-*N*-(6-Cyano-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran-4-yl)acetamide (43). A mixture of *trans*-*N*-(6-bromo-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran-4-yl)acetamide (**42**) (4.18 g, 14.6 mmol) and copper(I) cyanide (2.62 g, 29.2 mmol) in *N*-methylpyrrolidone (90 mL) was heated at 200 °C under argon for 3 h. The solvent was removed under vacuum, and the crude product was chromatographed on silica gel eluting with 5% methanol in ethyl acetate to obtain an off-white gum (3.12 g) which was triturated with isopropyl ether to afford the title compound (1.97 g, 58%) as an off-white solid, mp 194–195 °C: ^{1}H NMR (DMSO-d_6) δ 8.30 (d, J = 7.6 Hz, 1H), 7.63 (m, 2H), 6.97 (d, J = 8.8 Hz, 1H), 5.52 (d, J = 4.1 Hz, 1H), 4.73 (m, 1H), 4.16 (m, 2H), 3.82 (m, 1H), 1.87 (s, 3H); ^{13}C NMR δ 169.18, 158.16, 135.55, 132.84, 123.48, 119.28, 117.78, 102.98, 67.45, 64.60, 48.53, 22.93.

G. *trans*-4-Amino-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran-6-carbonitrile (32g). A solution of *trans*-*N*-(6-cyano-3,4-dihydro-3-hydroxy-2*H*-1-benzopyran-4-yl)acetamide (**43**) (1.94 g, 8.35 mmol) in a mixture of dioxane (25 mL) and 2.5 N sulfuric acid (22 mL) was heated at 75 °C for 60 h. The reaction mixture was concentrated under vacuum, made basic (pH > 11) with 50% NaOH solution, and extracted with ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4, and the solvent was evaporated. The crude product was crystallized from hexane–ethyl acetate to afford the title compound (1.15 g, 72%) as a white solid, mp

162–163 °C: ^{1}H NMR (DMSO-d_6) β 7. 79 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 5.29 (br s, 1H), 4.28 (d, J = 9.4 Hz, 1H), 4.04 (dd, J = 4.7 and 11.1 Hz, 1H), 3.65 (m, 2H), 2.09 (br s, 2H); ^{13}C NMR (DMSO-d_6) δ 157.45, 134.90, 131.76, 127,39, 119.35, 117.08, 102,13, 67.35, 66.86, 51.08.

N″-Cyano-N-(6-cyano-2,2-dimethyl-2H-1-benzopyran-4-yl)-N′-phenylguanidine (19). A. *trans*-N-[3-(Acetyloxy)-6-cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-yl]-N′-phenylguanidine (21). A solution of *trans*-N″-cyano-N-(3,4-dihydro-3-hydroxy-2,2-dimethyl-6-cyano-2H-1-benzopyran-4-yl)-N′-phenylguanidine (**8**) (2.52 g, 6.98 mmol) and acetic anhydride (1.0 g, 9.8 mmol) in pyridine (25 mL) was stirred for 60 h at room temperature. The crude reaction mixture was partitioned between ethyl acetate and 5% hydrochloric acid. The organic layer was washed with water, saturated sodium bicarbonate solution, and brine and dried over anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was recrystallized from ethanol to obtain the title compound (2.24 g, 79.4%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 9.36 (s, 1H), 7.63 (m, 3H), 7.35 (m, 2H), 7.20 (m, 3H), 6.97 (d, J = 8.8 Hz, 1H), 5.23 (m, 2H), 2.17 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.69, 158.69, 155.75, 136.95, 132.94, 132.66, 129.03, 125.28, 124.25, 123.79, 118.86, 118.09, 116.62, 103.31, 78.43, 72.07, 49.49, 25.85, 20.67, 19.54.

B. N″-Cyano-N-(6-cyano-2,2-dimethyl-2H-1-benzopyran-4-yl)-N′-phenylguanidine (19). A solution of *trans*-N-[3-(acetyloxy)-6-cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-yl]-N′-phenylguanidine (**21**) (0.99 g, 2.45 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.87 g, 12.27 mmol) in toluene (10 mL) was stirred at room temperature for 24 h. The reaction mixture was concentrated under vacuum and the residue partitioned between 10% citric acid solution and chloroform. The organic layer was separated, and the aqueous phase was reextracted with chloroform. The combined extracts were washed with water and brine and dried over anhydrous sodium sulfate. The solvent was evaporated, and the residue was crystallized from CH_2Cl_2/MeOH to obtain the title compound (0.541 g, 64.3%) as a yellow solid: ^{1}H NMR (DMSO-d_6) δ 11.83 (br s, 1H), 9.62 (s, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.68–7.39 (m, 3H), 7.27 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 8.2 Hz, 1H), 5.59 (s, 1H), 1.29 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 158.95, 155.58, 137.24, 134.16, 133.35, 130.35, 129.60, 128.77, 128.16, 120.45, 118.98, 117.45, 116.44, 110.83, 101.79, 57.99, 28.67.

The synthesis of **20** from **9** was carried out in an identical manner.

***trans*-N′-(6-Amino-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N″-cyano-N-phenylguanidine (14).** A solution of *trans*-N′-(6-nitro-3,4-dihydro-3-hydroxy-2,2-dimethyl-2H-1-benzopyran-4-yl)-N″-cyano-N-phenylguanidine[6] (1.05 g, 27.5 mmol) in ethanol (65 mL) was hydrogenated at atmospheric pressure using 5% palladium on carbon catalyst (0.1 g). The catalyst was filtered off, and the filtrate was evaporated *in vacuo* to obtain an orange solid. The crude product was chromatographed on silica gel eluting with ethyl acetate–hexane–ethanol (7:2.5:0.5), and the residue was triturated with isopropyl ether to give the title compound (0.38 g, 40%) as an off-white solid: ^{1}H NMR (trifluoroacetic acid-d_1) δ 7.60–7.97 (m, 9H), 7.39 (d, J = 9.4 Hz, 1H), 5.49 (d, J = 9.4 Hz, 1H), 4.52 (d, J = 8.2 Hz, 1H), 1.86 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (trifluoroacetic acid-d_1) δ 161.88, 154.42, 145.50, 137.30, 131.21, 128.56, 126.94, 125.74, 125.27, 124.97, 124.30, 119.98, 81.01, 74.60, 54.22, 27.44, 19.11.

Biological Assays. Antiischemic Potency. Male Sprague–Dawley rats were anesthetized using 100 mg/kg sodium pentobarbital (intraperitoneal), and heparin (1000 U/kg) was injected intravenously. While being mechanically ventilated, the hearts were perfused *in situ* via retrograde cannulation of the aorta. The hearts were then excised, moved to a Langendorff apparatus, and perfused with oxygenated Krebs–Henseleit solution containing (in mM): 112 NaCl, 25 $NaHCO_3$, 5 KCl, 1.2 $MgSO_4$, 1 KH_2PO_4, 1.25 $CaCl_2$, 11.5 glucose, and 2 pyruvate at a constant perfusion pressure (85 mmHg). A water-filled latex balloon was inserted into the left ventricle and connected to a Gould Statham pressure transducer (Gould Inc., Oxnard, CA) for measurement of left ventricular pressure. End diastolic pressure (EDP) was adjusted to 5 mmHg, and this balloon volume was maintained for the duration of the experiment. Preischemia or predrug contractile function, heart rate (HR), and coronary flow (extracorporeal electromagnetic flow probe; Carolina Medical Electronics, King, NC) were measured. The hearts were pretreated with vehicle (0.04% dimethyl sulfoxide, DMSO) or 1–30 μM test compound (except **18** which was tested up to 200 μM) (n = 4/group). The respective drug or vehicle treatment was continued for 10 min prior to the initiation of ischemia, and the agents were administered as a solution in the perfusate. Global ischemia was instituted by completely shutting off the perfusate flow, and the time to the onset of contracture was measured as the time necessary to increase end diastolic pressure by 5 mmHg. EC_{25} values for increasing time to contracture were determined from the regression analysis of the logarithmic fit of the concentration vs time-to-contracture, as previously described.[8]

Vasorelaxant Potency. To compare the antiischemic vs peripheral vasodilator activities, the effect on methoxamine-induced aortic constriction was determined. Male Wistar Kyoto rats were sacrificed using CO_2. Aortic rings (3 mm width) were cut, denuded of endothelium, and mounted in 20 mL muscle chambers containing an oxygenated solution of the following composition (in mM): 118.4 NaCl, 4.7 KCl, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 1.9 $CaCl_2$, 25.0 $NaHCO_3$, 10.1 glucose, and 0.01 mM Na_2EDTA maintained at 37 °C. The rings were stretched to 2 g preload during the equilibration period. Aortic rings were contracted with 0.3 μM methoxamine and steady state force of contraction was measured. Cumulative concentration–response curves for the test compounds (0.01–100 μM) were determined by adding them to the individual baths. IC_{50} values were determined from a quadratic fit to the logit transformation of the concentration–relaxation curves, as described previously.[7]

Supplementary Material Available: NMR data and chemical analyses of compounds **10–31** and intermediates (10 pages). Ordering information is given on any current masthead page.

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JM950024U