Cardioselective Antiischemic ATP-Sensitive Potassium Channel (K_{ATP}) Openers. 5. Identification of 4-(*N*-Aryl)-Substituted Benzopyran Derivatives with High Selectivity

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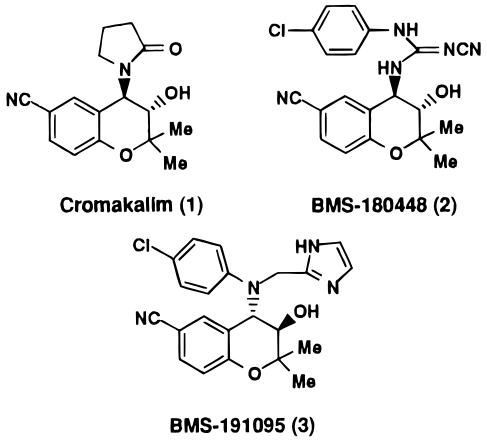
This paper describes our studies aimed at the discovery of structurally distinct analogs of the cardioprotective K_{ATP} opener BMS-180448 (**2**) with improved selectivity for the ischemic myocardium. The starting compound **6,** derived from the indole analog **4**, showed good cardioprotective potency and excellent selectivity compared to **2** and the first-generation K_{ATP} opener cromakalim (**1**). The structure−activity studies indicate that increasing the size of the alkyl ester leads to diminished potency as does its replacement with a variety of other groups (nitrile, methyl sulfone). Replacement of the ethyl ester of **6** with an imidazole gave the best compound **3** (BMS-191095) of this series which maintains the potency and selectivity of its predecessor **6**. The results described in this publication further support that there is no correlation between vasorelaxant and cardioprotective potencies of K_{ATP} openers. Compound **3** is over 20- and 4000-fold more selective for the ischemic myocardium than **2** and cromakalim (**1**), respectively. The selectivity for the ischemic myocardium is achieved by reduction of vasorelaxant potency rather than enhancement in antiischemic potency. As for cromakalim (**1**) and **2**, the cardioprotective effects of compound **3** are inhibited by cotreatment with the K_{ATP} blocker glyburide, indicating that the K_{ATP} opening is involved in its mechanism of cardioprotection. With its good oral bioavailability (47%) and plasma elimination half-life (3 h) in rats, compound **3** offers an excellent candidate to investigate the role of residual vasorelaxant potency of **2** toward its cardioprotective activity *in vivo*.

Introduction

The ATP-sensitive potassium channel (K_{ATP}) openers have been found to have direct cardioprotective properties independent of their vasodilating actions.[1] The cardioprotection afforded by these agents is inhibited by structurally different K_{ATP} blockers, indicating that K_{ATP} opening is involved in their protective actions.[2] The K_{ATP} openers show cardioprotective activity at concentrations that cause little cardiodepression, unlike, for example, calcium channel blockers (e.g., diltiazem).[3] However, in order to show efficacy in whole animal models, the first-generation compounds (e.g., cromakalim) have to be given directly into the coronary artery[4] to avoid peripheral vasodilation which can cause underperfusion of the tissue already at risk.[5] Thus, they have a narrow window of safety for the treatment of myocardial ischemia. The interest in K_{ATP} openers as cardioprotective agents is also highlighted by recent studies indicating that the K_{ATP} openers might mimic the beneficial effects of myocardial preconditioning.[6] Using the K_{ATP} blocker glyburide as a tool, a number of invesitigators have shown that the opening of the K_{ATP} is involved in mediating the cardioprotective actions of preconditioning in animal models[7] and humans.[8] The protective effects of K_{ATP} openers are not unique to the myocardium as they also mimic the neuronal protective effects of cerebral ischemic preconditioning in hippocampal neurons.[9] Thus, opening of the K_{ATP} may be part of an endogenous protective mechanism to minimize injury following ischemia.

We have shown that no correlation exists between cardioprotective and vasorelaxant potencies of K_{ATP} openers.[10] Further work aimed at the discovery of K_{ATP} openers selective for the ischemic myocardium led to the discovery of BMS-180448 (**2**) which shows enhanced selectivity compared to the first-generation agents (e.g., cromakalim). Unlike cromakalim which had to be given directly into the coronary artery to observe cardioprotection *in vivo*, **2** shows excellent cardioprotection on iv



administration.[11] Although more selective for the ischemic myocardium compared to the reference agents (e.g., cromakalim), compound **2** retains some degree of vasorelaxant activity (Table 1). To delineate the role

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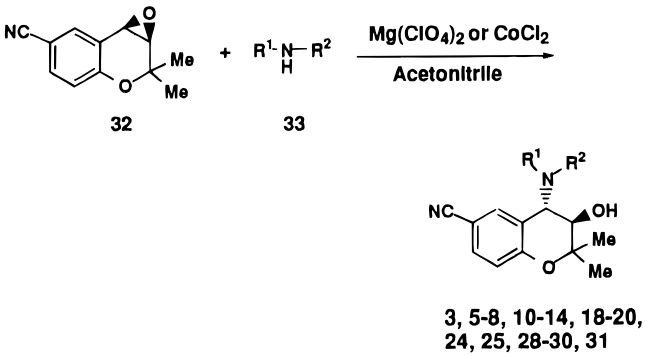
Scheme 1



of the residual vasorelaxant activity of **2** toward its cardioprotective efficacy, we set out to find agents that were nearly devoid of vasorelaxant activity. This publication details the results of those studies. We identified a structurally distinct analog, **3** (BMS-191095), of **2** which is over 20-fold more selective for the ischemic myocardium than compound **2**.

Chemistry

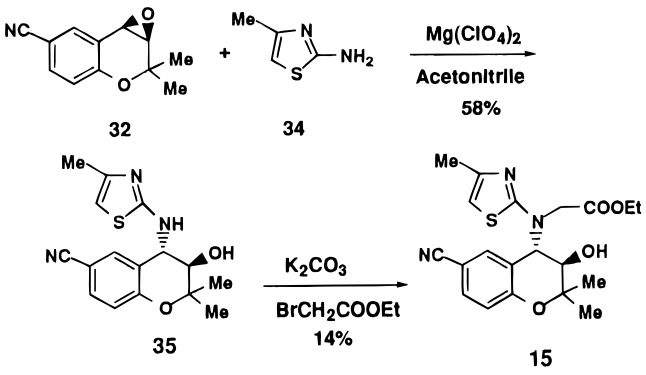
Most of the analogs (**5**−**8**, **10**−**14**, **18**−**20**, **24**, **25**, **29**) were prepared by opening the known epoxide **32**[12] with appropriately substituted aniline derivatives **33** in the presence of magnesium perchlorate in acetonitrile (Scheme 1).[13] The yield of this reaction is critically dependent on the concentration of the reaction mixture. The reaction proceeds in a high yield (96%) when the reactants are mixed in the presence of a minimum amount of acetonitrile (i.e., paste). Dilution of the reaction mixture usually results in longer reaction times and a reduction of yield. Lower yields of some of the products reflect reactions performed under dilute conditions prior to noticing the effect of concentration (Table 3).

While the magnesium perchlorate-induced opening of the epoxide **32** with aniline derivatives **33** was successful for the preparation of a wide variety of compounds (Table 3), it failed to provide the imidazole analogs **3**, **28**, **30**, and **31**. The use of cobalt chloride in place of magnesium perchlorate provided the requisite imidazole derivatives **3**, **28**, **30**, and **31** in modest yields (24−55%) (Scheme 1).[14] The success of this reaction is dependent on the quality of cobalt chloride. We usually dried the commercially available cobalt chloride prior to its use, as the use of material directly out of a bottle gave lower yields of the products.

The aniline derivatives **33** used for the opening of epoxide **32**[12] can be readily obtained from suitably substituted anilines by either reductive amination with aldehydes or alkylation with suitable electrophiles. Selective procedures are described in the Experimental Section.

A more convergent approach for the preparation of analogs of **6** which involves the alkylation of the protio derivative **8** was somewhat less successful, presumably due to the low reactivity of the aniline nitrogen in **8** and potential interference by the C3-hydroxyl. The only compound prepared by this method was the thiazole analog **15** (Scheme 2) which could not be obtained by the route outlined in Scheme 1. The intermediate **35**, obtained by opening of the epoxide **32** with 2-amino-4-methylthiazole (**34**), was alkylated with ethyl bromoacetate to provide the desired product **15** in a low overall yield.

Scheme 2



The benzoxazole derivative **16** was prepared according to the procedure outlined in Scheme 3. The amino alcohol **36**[10] was subjected to reductive amination with ethyl glyoxalate in the presence of sodium cyanoborohydride to provide the ester **37** in 48% yield. The ester **37** was treated with 2-chlorobenzoxazole in the presence of sodium hydride, and the resulting O-alkylated material **38** was treated with acetic acid to provide the desired product **16**. Details of this method which involves the intramolecular O- to N-migration (**38** → **16**) of the benzoxazole moiety are published.[15]

The *N*-acetyl analog **22** was prepared according to the method outlined in Scheme 4. The phthalamido-protected compound **39**, prepared from the epoxide **32** in the usual manner (magnesium perchlorate, acetonitrile, heat, 67%), was deprotected by treatment with methylhydazine to give the amine **40** in a quantitative yield. The amine **40** was acetylated under standard conditions (AcCl, pyridine) to provide **22** in 85% yield.

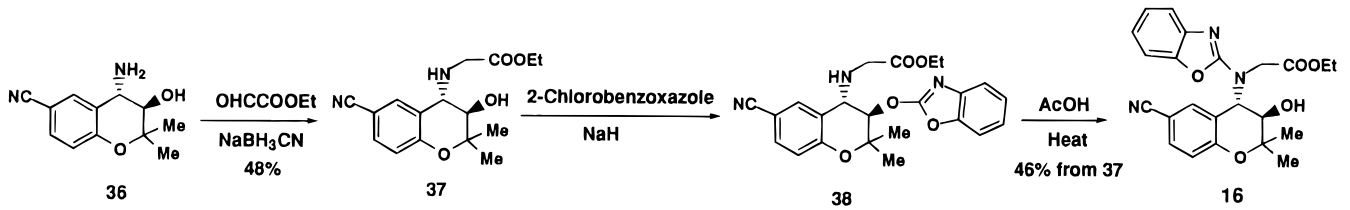
The synthesis of the oxalate derivative **23** is summarized in Scheme 5. The amino alcohol **41** was prepared by treatment of the epoxide **32**[12] with 4-fluoroaniline in the presence of magnesium perchlorate. The hydroxyl group in **41** was protected as a 4-methoxybenzyl ether, and the resulting product **42** was acylated (ethyl oxalyl chloride, 4-(dimethylamino)pyridine) to provide the oxalate derivative **43** in 76% yield. The 4-methoxybenzyl ether was cleaved by treatment with trifluoroacetic acid to provide the desired product **23** in 55% yield. The protection of the hydroxyl group in **41** was necessitated due to the competing O-acylation of **41** which we were unable to suppress.

The synthesis of **9**, **17**, and **26** from the ester **6** is outlined in Scheme 6. The acid analog **9** was obtained in excellent yield by simple saponification (LiOH, THF) of the ester **6**. The ethylamide analog **17** was obtained in 70% yield by treatment of the ester **6** with ethylamine. The oxadiazole derivative **26** was prepared in 61% yield by treatment of the ester **6** with *N*-hydroxyacetamidine in the presence of sodium hydride.

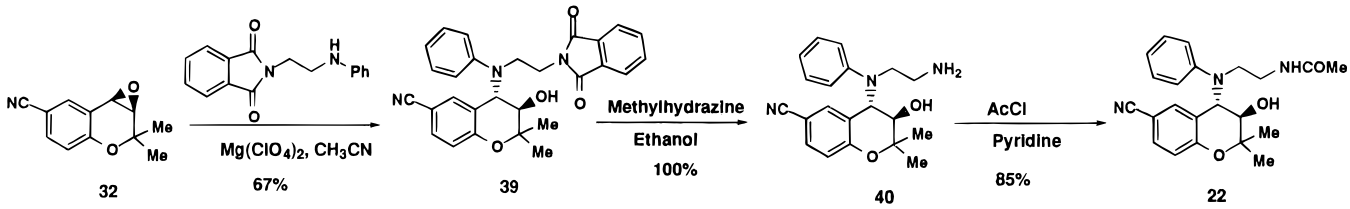
The oxazole analog **27** was obtained from the ester **6** in three steps (Scheme 7). The ester **6** was heated with 2,2-dimethoxyethylamine to give the amide **44** in 96% yield. The dimethyl acetal in **44** was cleaved (aqueous HCl, THF), and the resulting aldehyde **45** was immediately cyclized to the oxazole **27** in low (12%) overall yield.

The ^{1}H and ^{13}C NMR spectra of most of the analogs show broad signals at room temperature due to a restricted rotation around the C4−N bond. Heating the

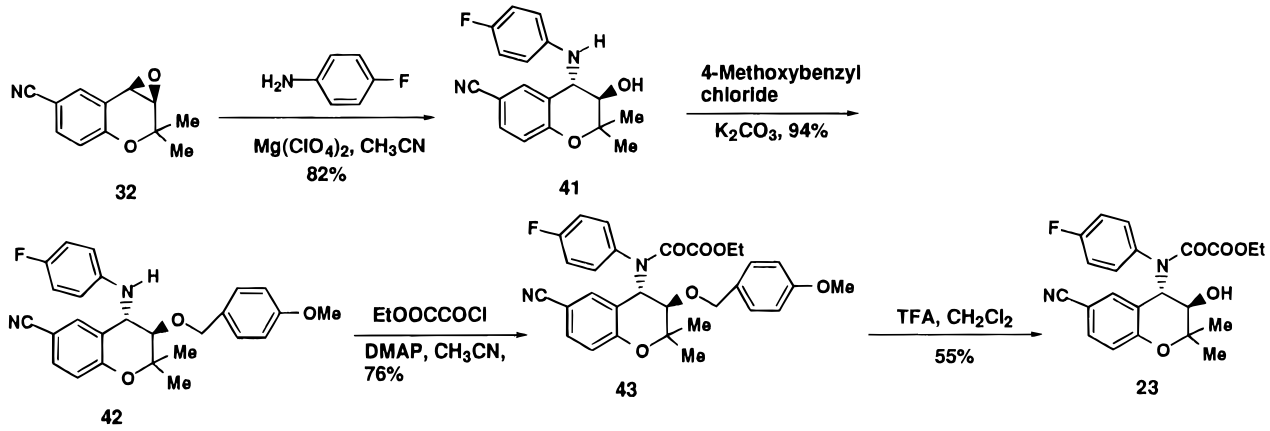
Scheme 3



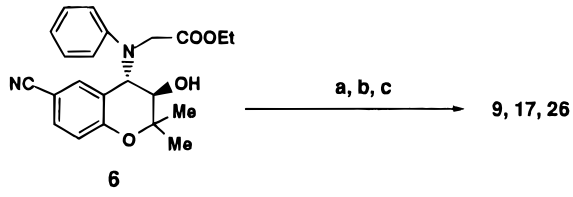
Scheme 4



Scheme 5



Scheme 6[a]



[a] Reaction conditions: (a) for **9**, lithium hydroxide, THF, water, 80%; (b) for **17**, ethylamine, methanol, 70%; (c) for **26**, *N*-hydroxyacetamidine, NaH, THF, heat, molecular sieves, 61%.

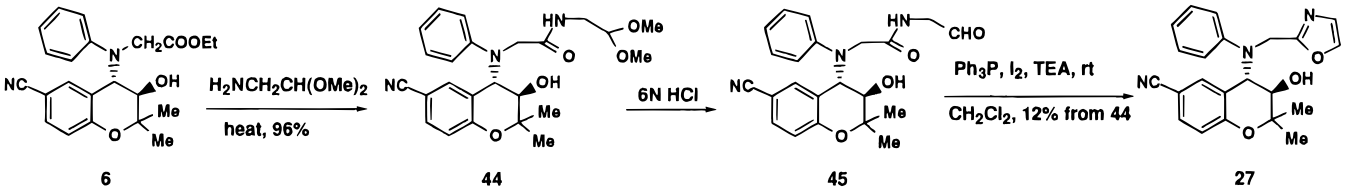
sample up to 100 °C in dimethyl sulfoxide usually gave a well-resolved spectrum.

Results and Discussion

Discovery of the Lead Compound. The cardioprotective (also referred to as 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 perfused rat hearts.[16] Time to contracture is defined as the time necessary during total global ischemia to increase end diastolic pressure by 5 mmHg compared to the baseline value.[16] Contracture develops due to rigor bond formation resulting from depletion of ATP. Compounds were initially screened at 10 μM concentration. Those showing greater than 25% increase in time to the onset of contracture were subjected to concentration−response studies to determine EC_{25} values. Vasorelaxant potencies were determined by measurement of IC_{50} values for relaxation of the rat aorta preconstricted with methoxamine.[17] Details of these assays are described.[18] The ratio of the 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 *in vitro* tests are different from each other (isolated rat heart vs agonist-constricted rat aorta), the ratio does not indicate absolute selectivity. It only serves as a useful index to select compounds for evaluation *in vivo*. Validity of these *in vitro* test systems to predict antiischemic selectivity *in vivo* has been demonstrated by detailed studies with **2** and cromakalim (**1**).[11]

The starting point for the identification of a lead compound was the indole analog **4** which showed modest antiischemic potency with excellent cardiac selectivity (Table 1).[19] Although **4** had all the desirable features to serve as a lead compound, the synthesis of **4** and its analogs presented a major synthetic challenge. For example, the formation of the desired product **4** from epoxide **32** is accompanied by the dehydration product.[19] Therefore, efforts were undertaken to prepare simplified analogs of this compound by breaking various indole bonds (Scheme 8).[20] That exercise led to the identification of compound **5** with slightly superior cardioprotective potency relative to compound **4** (Table 1). Since **5** possesses little vasorelaxant activity ($IC_{50} > 30$ μM), it is more selective than **2** for the ischemic myocardium. Most of the antiischemic activity of **5** resides in the 3*R*,4*S*-enantiomer **6**, as the 3*S*,4*R*-enantiomer **7** is significantly less potent than **6** as an antiischemic agent.

Scheme 7



6 44 45 27

Table 1. Vasorelaxant and Antiischemic Potencies of Compounds **1, 2**, and **4**−**7**

compd	antiischemic potency[a] EC_{25} (μM) or % incorp @ 10 μM	vasorelaxant potency[b] IC_{50} (μM)	ratio EC_{25}/IC_{50}
1 (racemic)	8.9	0.032 (0.021, 0.04)	278
2 (3*S*,4*R*)	2.5	1.8 (0.78, 4.25)	1.4
4 (racemic)	8.1	33 (19.0, 58.6)	0.25
5 (racemic)	4.7	>30[c]	<0.17
6 (3*R*,4*S*)	2.2	>30[c]	<0.07
7 (3*S*,4*R*)	5%	>30[c]	

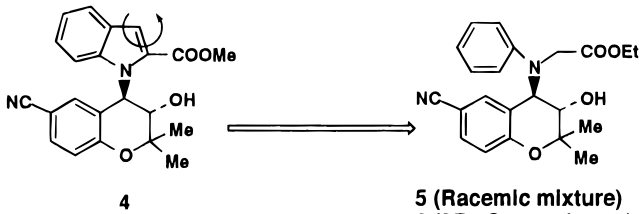
[a] EC_{25} for antiischemic (cardioprotective) potency is determined by measurement of increase in time to contracture in globally ischemic isolated perfused rat hearts. Time to contracture is defined as the time necessary during total global ischemia to increase end diastolic pressure by 5 mmHg. Each point on the concentration−response curve is an average of three to four determinations, and the IC_{50} value is within ±20%. [b] IC_{50} for vasorelaxant potency is determined by relaxation of rat aorta precontracted with methoxamine. IC_{50} value is presented as a mean with 95% confidence interval in parentheses; $n = 4$ or higher. [c] Concentrations higher than 30 μM could not be tested due to limitation of solubility.

It is of interest to note that the absolute stereochemistry of **6** is opposite to that of **2** and cromakalim (**1**). The reasons for this reversal of absolute stereochemical requirements for **6** are not known at the present time. They may be related to its different mode of binding to the receptor site(s) compared to **2** and cromakalim (**1**). The higher cardiac selectivity of **6** and its significantly altered structure (opposite stereochemistry, no cyanoguanidine) compared to **2** made it attractive for further structure−activity work.

Structure−Activity Relationships. Since cardioprotective and vasorelaxant potencies define selectivity, we studied the effect of structural changes on both parameters. We concentrated on making changes to the structural moiety ($PhNCH_2COOEt$) attached to C4 of the benzopyran ring in **6** (Table 2). The detailed structure−activity relationships for the benzopyran portion of **2** are published.[18] Comparison between **6** (3*R*,4*S*) and the protio analog **8** (racemate) indicates that the second substituent on the aniline nitrogen contributes little to antiischemic potency although it enhances cardiac selectivity by reducing vasorelaxant potency. The carboxylic acid analog **9**, a putative metabolite of **6**, is devoid of antiischemic activity. Chain-extended esters **10** and **11** offer no further improvement in the antiischemic potency of **6**. Further increase in the size of the ester group, as in the *n*-butyl analog **12**, causes attenuation of antiischemic potency.

The 4-fluoro (**13**)- and 4-chloro (**14**)-substituted analogs of **6** retain antiischemic potency indicating that the pendant aromatic ring of **6** can be substituted without adversely affecting antiischemic potency. While replacement of the pendant phenyl ring with methylthiazole (**15**) maintains significant antiischemic activity, the corresponding benzoxazole analog **16** is devoid of

Scheme 8



4

5 (Racemic mixture)
6 (3R,4S-enantiomer)
7 (3S,4R-enantiomer)

antiischemic activity. Lack of antiischemic activity in **16** compared to **15** and **6** indicates that there are restrictions as to the size of the pendant aryl/heterocyclic ring of **6**.

Since the ethyl ester of **6** was expected to be metabolically labile (the acid **9** being inactive), a major portion of our effort was devoted to preparing stable surrogates for the ester group of **6**. Replacement of the ester with an amide (**17**), ether (**18**), or nitrile (**19**) led to a reduction in cardioprotective potency. The phosphonate analog **20** has cardioprotective potency similar to the ethyl ester **6**. Although a direct sulfone analog of **6** could not be prepared due to synthetic difficulty, the homologous sulfone **21** is less potent than **6**. The *N*-acetyl analog **22** also shows reduced cardioprotective potency relative to **6**. These results indicate that narrow structure−activity relationships exist in this portion of the molecule. This conclusion is also supported by the lower cardioprotective potency of the carbonyl (**23**) replacement for the side chain methylene group of **6**. Comparison between **6**, **23**, and **24** also suggests that an sp^3 carbon and nitrogen atoms adjacent to the aniline nitrogen are preferred.

The most gratifying results for replacing the ethyl ester of **6** with potentially metabolically stable surrogates were obtained with heterocyclic analogs. While the furan analog **25** has cardioprotective potency similar to the ester **6**, the oxadiazole **26** is slightly less potent than **6**. Both the oxazole (**27**) and imidazole (**28**) analogs retain the cardioprotective potency of **6**. The isoxazole analog **29** shows diminished potency relative to the parent ester **6**. Based on its potency and selectivity, the imidazole analog **28** was selected for further modifications. The 4-fluorophenyl- and 4-chlorophenyl-substituted imidazoles **30** and **3**, respectively, prepared to suppress potential hydroxylation *in vivo* of the pendant phenyl ring, retain the full antiischemic potency of their parent **28**. The 4-chlorophenyl imidazole analog **3** is the most potent compound of this series. Similar to the prototype ester **6**, most of the cardioprotective activity resides in the 3*R*,4*S*-enantiomer **3**, as the 3*S*,4*R*-enantiomer (**31**) of **3** has little antiischemic activity up to a concentration of 10 μM. Thus, changing the ester (**6**) to an imidazole (**3**) does not affect the absolute stereochemical requirements for the cardioprotective activity of this series of compounds. By virtue

of having low vasorelaxant potencies, most compounds of this series show excellent selectivity for the ischemic myocardium (Tables 1, 2).

Compound **3** is slightly more potent than **2** as a cardioprotectant. Having very little vasorelaxant activity up to a concentration of 30 μM, it is at least 20-fold more cardiac selective than **2**. Compound **3** is over 4000-fold more selective than the first-generation agent cromakalim (**1**). The selectivity for the ischemic myocardium is achieved by reduction of vasorelaxant potency as the cardioprotective potency remains relatively constant (Tables 1, 2). These results indicate that the structure−activity relationships for the vasorelaxant and antiischemic potencies are distinct. We have no explanation for these differences except that the vasorelaxant and cardioprotective effects of K_{ATP} openers might be mediated via different receptors. We need to understand the molecular mechanism of action of K_{ATP} to explain our experimental observations.

With the identification of compound **3**, we achieved our objective of finding a more cardiac selective agent than **2**. We further characterized **3** for its mechanism of action and metabolic stability before evaluating its efficacy *in vivo*. Both these factors can potentially impact the results of studies *in vivo*.

Since there are significant differences (absolute stereochemistry, C4 moiety) between the structures of **2** and **3**, it was important to confirm the K_{ATP}-opening mechanism for the cardioprotective activity of **3**. This is especially important as our assay measuring cardioprotective potency in isolated rat hearts is not based on the mechanism of action of K_{ATP} openers. The receptor site(s) relevant to cardioprotection being unknown, the biochemical tools to carry out the mechanism studies on cardioprotective K_{ATP} openers are limited at the present time. The mechanistic work is usually carried out through pharmacological and electrophysiological studies. The currently available tools for pharmacological studies are the sulfonylurea class of K_{ATP} blockers (e.g., glyburide) which abolish the cardioprotective effects of K_{ATP} openers in isolated perfused hearts.[21] The concentrations of K_{ATP} blockers that abolish the cardioprotective effects of K_{ATP} openers have no effects in the isolated hearts when given alone.[21]

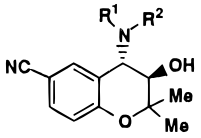
Effect of the K_{ATP} Blocker Glyburide on Cardioprotection by Compound 3. We studied the effect of the K_{ATP} blocker glyburide on the cardioprotective effects of **3** as measured by the increase in time to the onset of ischemic contracture in isolated rat hearts. The globally perfused rat hearts were divided into five groups: vehicle, **3** (6 μM), **3** (6 μM) + glyburide (0.3 μM), diltiazem (1 μM), and diltiazem (1 μM) + glyburide (0.3 μM). The calcium channel blocker diltiazem was included in this study to ensure the specificity of the K_{ATP} blocker glyburide. The test agents were given in the perfusion medium 10 min prior to the cessation of flow. The time to contracture is defined as the time necessary during total global ischemia to increase end diastolic pressure by 5 mmHg compared to the baseline value. In control hearts, the contracture develops in approximately 17 min which is significantly enhanced (23 min) by pretreatment with 6 μM **3** (Figure 1). This increase in time to the onset of contracture is abolished by cotreatment with 0.3 μM glyburide (22.8 $\pm$ 0.3 vs 17.6 $\pm$ 0.5 min). This concentration of glyburide has no effect on the vehicle-treated hearts (data not shown).[21] As shown in Figure 1, glyburide has no effect on the cardioprotective effects of the calcium channel blocker diltiazem (time to contracture: 23.7 vs 24 min). Thus, glyburide appears to be specific for abolishing the cardioprotective actions of **3**. We have previously shown that glyburide does not affect the cardioprotective benefits of a diverse group of cardioprotectants acting via mechanisms other than the K_{ATP} opening.[21] These data suggest that the cardioprotection afforded by **3** and its analogs in the isolated perfused rat hearts is most likely due to the opening of the K_{ATP} in the heart. Although the nature of the molecular interaction between the K_{ATP} openers (e.g., **3**) and glyburide is not known at the present time, it is clear that the glyburide-binding ABC-type protein (SUR) is part of the K_{ATP} complex.[22]

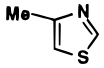
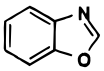
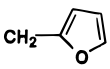
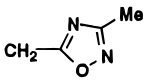
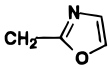
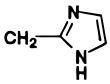
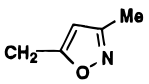
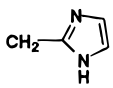
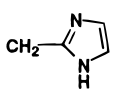
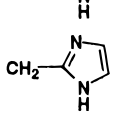
Bioavailability and Pharmacokinetics of Compound 3. Since metabolism and pharmacokinetics can impact the results of studies *in vivo*, we evaluated the oral bioavailability and plasma half-life of **3** in rats. Male rats were given single intravenous or oral doses (30 μmol/kg, $N = 4$) of compound **3** as a solution in ethanol:PEG 400:water (2:3:5). Serial plasma samples were analyzed by a specific LC/MS method developed for **3**. After intravenous administration, **3** was eliminated from plasma with apparent biphasic kinetics (Figure 2). The apparent terminal elimination half-life ($t_{1/2\beta}$) was 3.0 h. Following an oral dose of compound **3** (30 μmol/kg), the maximal plasma concentration of **3** (C_{max}) was 1.3 μM and was observed at a T_{max} of 1.9 h. Based upon AUC values, bioavailability of **3** after oral doses was estimated to be about 47%. Thus, **3** has a modest half-life (3 h) and good oral bioavailability (47%) in rats.

Conclusion

The objective of our work was to find a structurally distinct analog of BMS-180448 (**2**) with enhanced cardiac selectivity. We have shown that the modest selectivity of **2** for the ischemic myocardium can be further increased by structural modifications of **6** which was derived from the indole analog **4**. The structure−activity studies indicate that increasing the size of the alkyl ester leads to diminished potency as does its replacement with a variety of other groups such as acetonitrile and methyl sulfone. The ester can be successfully replaced with some heterocycles (e.g., imidazole, oxazole). The best compound of this series is the 4-chlorophenyl imidazole analog **3** (BMS-191095) which shows enhanced selectivity for the ischemic myocardium compared to its predecessor **2**. Notably, the biological stereoselectivity of **3** (3*R*,4*S*) and its congeners is opposite to that of **2** (3*S*,4*R*). The results described in this publication further support that there is no correlation between vasorelaxant and cardioprotective potencies of K_{ATP} openers. While compounds **2** and **3** show greater than 20-fold separation in their vasorelaxant potencies, the two compounds show similar "glyburide-sensitive" cardioprotective potencies. The improved cardiac selectivity of **3**, as measured by the ratio of cardioprotective and vasorelaxant potencies, might translate into a wider window of safety for the treatment of myocardial ischemia. With its good oral bioavailability (47%) and plasma elimination half-life (3 h), compound **3** offers an excellent candidate to probe

Table 2. Vasorelaxant and Antiischemic Potencies of Analogs of **6** (All compounds except **8**, **9** (racemic), and **31** (3*S*,4*R*) have 3*R*,4*S*-stereochemistry)



Compound	R^1	R^2	Antiischemic Potency[a] EC_{25} (μM) or % inc. @ 10 μM	Vasorelaxant Potency[b] IC_{50} (μM)	Ratio[c] EC_{25}/IC_{50}
6	Ph	CH_2COOEt	2.2 (38%)	>30[c]	<0.07
8 (racemic)	Ph	H	3.9	1.2 (0.84, 1.6)	3.9
9 (racemic)	Ph	CH_2COOH	0%	>100	
10	Ph	CH_2CH_2COOEt	26%	54 (24.7, 119)	
11	Ph	$CH_2(CH_2)_2COOEt$	5.7	>30	
12	Ph	CH_2COO-nBu	8%	27 (13.6, 51.8)	
13	4F-Ph	CH_2COOEt	3.8	>30	<0.017
14	4Cl-Ph	CH_2COOEt	6.5	>30	<0.22
15		CH_2COOEt	7.8	84 (38.8, 183)	<0.09
16		CH_2COOEt	0%	>30	
17	Ph	$CH_2CONHEt$	21%	>30	
18	Ph	CH_2CH_2OMe	15%	>30	
19	Ph	CH_2CN	8%	59 (26.2, 158.6)	
20	4F-Ph	$CH_2PO(OEt)_2$	4.9	47 (28.4, 76.3)	0.104
21	Ph	$CH_2CH_2SO_2Me$	0%	27 (21, 33)	
22	Ph	CH_2CH_2NHAc	5%	>30	
23	4F-Ph	COCOOEt	0%	43 (33, 53)	
24	Ph	NHCOOEt	4.3	2.2 (1.8, 2.6)	1.95
25	Ph		3.2	12 (9.4, 14.9)	0.27
26	Ph		10	>30	<0.33
27	Ph		5.3	>30	<0.18
28	Ph		4.3	>30	<0.14
29	Ph		11%	>30	
30	4F-Ph		3.3	>30	0.11
3	4Cl-Ph		1.4	>30	<0.05
31 (3S, 4R)	4Cl-Ph		14%	>30	

[a] EC_{25} for antiischemic (cardioprotective) potency is determined by measurement of increase in time to contracture in globally ischemic isolated perfused rat hearts. Time to contracture is defined as the time necessary during total global ischemia to increase end diastolic pressure by 5 mmHg. Each point on the concentration-response curve is an average of three to four determinations, and the IC_{50} value is within ±20%. [b] IC_{50} for vasorelaxant potency is determined by relaxation of rat aorta precontracted with methoxamine. IC_{50} value is presented as a mean with 95% confidence interval in parentheses; $n = 4$ or higher. [c] For some analogs, concentrations higher than 30 μM could not be tested due to solubility limitations.

Table 3. Physical Properties of Compounds **3** and **5**−**31**

compd	conditions	yield (%)	mol formula	mp (°C)[a]	microanal.
3	$CoCl_2$	55	$C_{22}H_{21}ClN_4O_2 \cdot HCl$	226−228 (A)	C, H, N, Cl
5	$Mg(ClO_4)_2$	53	$C_{22}H_{24}N_2O_4$	140−144 (B)	C, H, N
6	$Mg(ClO_4)_2$	31	$C_{22}H_{24}N_2O_4 \cdot 0.37H_2O$	182−183 (B)	C, H, N
7	$Mg(ClO_4)_2$	20	$C_{22}H_{24}N_2O_4 \cdot 0.24H_2O$	182−183 (B)	C, H, N
8	$Mg(ClO_4)_2$	84	$C_{18}H_{18}N_2O_2 \cdot HCl \cdot 0.13Et_2O$	195−197 (B)	C, H, N, Cl
9			$C_{20}H_{20}N_2O_4 \cdot 0.1H_2O$	163−165 (B)	C, H, N
10	$Mg(ClO_4)_2$	96	$C_{23}H_{26}N_2O_4 \cdot 0.1H_2O$	62−63	C, H, N
11	$Mg(ClO_4)_2$	96	$C_{24}H_{29}N_2O_4 \cdot 0.1H_2O$	109−110	C, H, N
12	$Mg(ClO_4)_2$	65	$C_{24}H_{28}N_2O_4$	82−85	C, H, N
13	$Mg(ClO_4)_2$	37	$C_{22}H_{23}FN_2O_4$	195−197 (C)	C, H, N, F
14	$Mg(ClO_4)_2$	47	$C_{22}H_{23}ClN_2O_4$	172−173 (B)	C, H, N, Cl
15			$C_{20}H_{23}N_3SO_4 \cdot 1.3H_2O$	83	C, H, N
16			$C_{23}H_{23}N_3O_5 \cdot 0.3H_2O$	90	C, H, N
17			$C_{22}H_{25}N_3O_3$	213−214 (B)	C, H, N
18	$Mg(ClO_4)_2$	77	$C_{21}H_{24}N_2O_3$	119−124	C, H, N,
19	$Mg(ClO_4)_2$	39	$C_{20}H_{19}N_3O_2 \cdot 0.27H_2O$	85−90 (B)	C, H, N,
20	$Mg(ClO_4)_2$	35	$C_{23}H_{28}FN_2O_5P$	55−56	C, H, N, F, P
21			$C_{21}H_{24}N_2O_4S \cdot 0.6H_2O$	75−85	C, H, N, S
22			$C_{22}H_{25}N_3O_3 \cdot 0.21H_2O$	217−218 (D)	C, H, N
23			$C_{22}H_{21}FN_2O_5 \cdot 0.25C_6H_{14}$	122−123 (E)	C, H, N, F
24	$Mg(ClO_4)_2$	25	$C_{21}H_{23}N_3O_4$	161−162	C, H, N
25	$Mg(ClO_4)_2$	72	$C_{23}H_{22}N_2O_3$	134−135	C, H, N
26			$C_{22}H_{22}N_4O_3$	148−149 (B)	C, H, N
27			$C_{22}H_{21}N_3O_3 \cdot 1.0H_2O \cdot 0.14EtOAc$	207−208	C, H, N
28	$CoCl_2$	24	$C_{22}H_{22}N_4O_2 \cdot 0.94H_2O$	259−260 (F)	C, H, N
29	$Mg(ClO_4)_2$	60	$C_{23}H_{23}N_3O_3$	80−90	C, H, N
30	$CoCl_2$	41	$C_{22}H_{21}FN_4O_2 \cdot HCl \cdot 1.4H_2O$	lyophilate	C, H, N, F, Cl
31	$CoCl_2$	50	$C_{22}H_{21}ClN_4O_2 \cdot HCl$	224−226 (A)	C, H, N, Cl

[a] Solvents for crystallization: A, acetonitrile−toluene; B, hexanes trituration; C, EtOAc−hexanes; D, triturated with isopropyl ether; E, triturated with hexanes−ether; F, $CHCl_3$−hexanes.

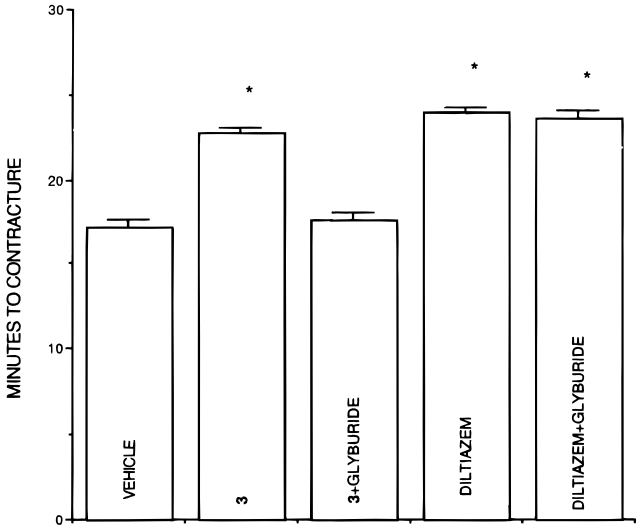


Figure 1. Effect of the K_{ATP} blocker glyburide on the cardioprotective effects of **3** (6 μM) and the calcium channel blocker diltiazem (1 μM) in isolated perfused globally ischemic rat hearts. While glyburide (0.3 μM) has no effect on the cardioprotective effects of diltiazem, it abolishes the cardioprotective actions of **3** as measured by the time to the onset of contracture. *Significantly different from vehicle-treated hearts.

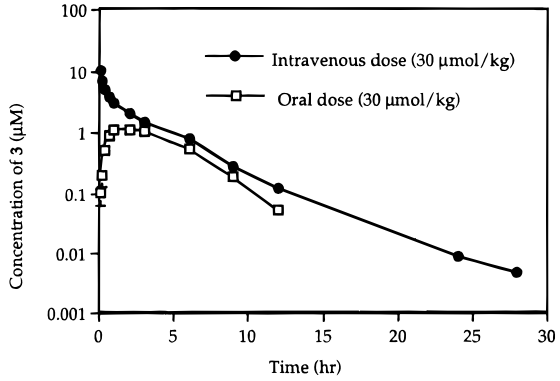


Figure 2. Mean plasma concentrations of (3*R*)-*trans*-4-[(4-chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile, monohydrochloride (**3**) after intravenous and oral doses to rats.

the role of residual vasorelaxant potency of **2** toward its cardioprotective activity *in vivo*. The results of those studies will be reported in future publications.

Experimental Section

Chemistry. All melting points were taken on a capillary melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer 983 spectrophotometer in KBr pellets. ^1H and ^{13}C NMR spectra were measured on JOEL GX-400 and FX-270 spectrometers with tetramethylsilane as an internal standard. Mass spectra were obtained with a Finnigan TSQ-4600 spectrometer. Flash chromatography was run with Whatman LPS-1 silica gel and Merck Kieselgel 60 (230−400 mesh ASTM). All compounds were characterized by ^1H and ^{13}C NMR and mass spectra. Microanalysis of all crystalline compounds is consistent with the structures assigned. The amount of solvent present in the molecular formula was determined by ^1H NMR spectra and microanalysis. Karl Fisher analysis was performed in selected cases to confirm the amount of water present.

Representative Procedure for the Magnesium Perchlorate-Promoted Reaction: Preparation of (3*R*)-*trans*-3-[*N*-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)phenylamino]propanoic Acid, Ethyl Ester (10). A mixture of 3-(*N*-phenylamino)propanoic acid, ethyl ester[23] (0.44 g, 2.3 mmol), epoxide **32**[12] (0.30 g, 1.5 mmol), and magnesium perchlorate (0.33 g, 1.5 mmol) in acetonitrile (0.3 mL) was allowed to stand at room temperature for 24 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel eluting with EtOAc/hexanes (1:12) to give a colorless solid (0.57 g, 96%): ^1H NMR ($CDCl_3$) δ 7.3−7.4 (m, 4H), 6.8−7.2 (m, 4H), 4.8 (d, J = 10.0 Hz, 1H), 4.0−4.1 (m, 3H), 3.6 (s, 2H), 3.2 (s, 1H), 2.7−2.8 (m, 1H), 2.5−2.6 (m, 1H), 1.6, 1.3 (s, 3H each), 1.2 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 157.2, 148.6, 132.6, 131.9, 129.6, 123.2, 119.7, 119.1, 118.6, 116.5, 103.5, 80.3, 70.0, 62.9, 60.9, 41.0,

32.2, 27.1, 18.8, 14.0. Compounds **5**−**8**, **11**−**14**, **18**−**20**, **24**, **25**, and **29** were prepared in a similar manner.

Representative Procedure for the Cobalt Chloride-Promoted Reaction: Preparation of (3*R*)-*trans*-4-[(4-Chlorophenyl)-*N*-(1*H*-imidazol-2-ylmethyl)amino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile, Monohydrochloride (3). A mixture of epoxide **32**[12] (40.0 g, 198.79 mmol), *N*-(4-chlorophenyl)-1*H*-imidazole-2-methanamine (41.3 g, 198.79 mmol), and anhydrous cobalt chloride (25.8 g, 198.79 mmol) in dry acetonitrile (160 mL) under argon was heated at 60 °C (oil bath temperature) for 28 h. The deep blue reaction mixture was allowed to cool to room temperature and treated with saturated sodium bicarbonate followed by ethyl acetate (1600 mL). The mixture was shaken and filtered through a sintered glass filter to remove solids. The organic layer was separated, washed with saturated sodium bicarbonate, and filtered through a short pad of Celite to remove additional solids. The aqueous layer was removed, and the yellow organic layer was washed with brine. It was dried (sodium sulfate), and the solvent was removed. The residue was heated with hexanes (∼1000 mL)/ethyl acetate (100 mL) and the colorless solid was collected. The solid was heated with methanol (2000 mL) for 15 min, cooled to room temperature, and filtered to provide the desired product as a white solid (44.72 g, 55%). This material was converted to its hydrochloride salt by treatment with ethereal HCl and crytallized from acetonitrile−toluene to provide **3** as a colorless powder: ^{1}H NMR (CD_3OD, 60 °C) δ 7.73 (d, J = 1.2 Hz, 1H), 7.67 (dd, J = 1.2, 8.8 Hz, 1H), 7.35 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 8.8 Hz, 2H), 5.15 (d, J = 10.0 Hz, 1H), 5.05 (d, J = 1.8 Hz, 2H), 4.71 (br s, 1H), 4.22 (d, J = 10.0 Hz, 1H), 1.68, 1.47 (s, 3H each); ^{13}C NMR (CD_3OD, 60 °C) 158.9, 147.6, 147.4, 134.5, 133.1, 130.4, 126.8, 124.5, 120.5, 120.1, 119.8, 118.9, 105.3, 82.1, 71.4, 63.4, 46.0, 27.3, 19.1. Compounds **28**, **30**, and **31** were prepared in a similar manner.

Representative Procedures for the Preparation of Compounds 33. 1. *N*-(4-Chlorophenyl)-1*H*-imidazole-2-methanamine, 33 (R^1 = 4Cl-Ph, R^2 = CH_2-2-imidazolyl). A mixture of 4-chloroaniline (66.65 g, 522.43 mmol) and 2-imidazolecarboxaldehyde (50.2 g, 522.43 mmol) in MeOH (1000 mL) was stirred at 55−60 °C for 16 h. The reaction mixture was cooled in an ice bath, treated with sodium borohydride (21.74 g, 574.67 mmol), and allowed to warm to ambient temperature. It was stirred for 2 h and concentrated to give a white emulsion. It was diluted with water (∼500 mL) and ethyl acetate (1200 mL). The organic layer was removed and the aqueous mixture reextracted with ethyl acetate (3 × 200 mL). The combined organic layers were washed with brine, dried (sodium sulfate), and concentrated to ∼500 mL of a brown solution containing some solid. The mixture was treated with hexane (∼200 mL) and stored in the freezer (−5 to 0 °C) for 2 h. The desired product was collected by filtration to give a colorless solid (83.36 g, 77%). ^{1}H NMR (DMSO-d_6, 50 °C) δ 11.80 (br s, 1H), 7.07 (ABq, J = 8.8 Hz, 2H), 6.91 (s, 2H), 6.65 (ABq, J = 8.8 Hz, 2H), 6.11 (br m, 1H), 4.22 (d, J = 5.3 Hz, 2H); ^{13}C (DMSO-d_6, 50 °C) 147.3, 145.5, 128.3, 121.5, 119.5, 113.7, 41.1. This material was used for the preparation of compounds **3** and **31**. Other aniline derivatives **33** prepared by this method were those used for the preparation of compounds **28** and **30**.

2. *N*-(2-Furanylmethyl)phenylamine, 33 (R^1 = Ph, R^2 = CH_2-2-furyl). A mixture of aniline (1.93 g, 20.0 mmol) and 2-furaldehyde (2.50 g, 26.8 mmol) in 1,2-dichloroethane (100 mL) under argon at 5 °C was treated with $Na(OAc)_3BH$ (5.65 g, 26.8 mmol) and acetic acid (1.5 mL) and stirred at room temperature overnight. The reaction mixture was concentrated, and the residue, diluted with ethyl acetate, was washed with sodium bicarbonate, water, and brine. The organic layer was dried over magnesium sulfate and concentrated. The product was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (20:1) to give an oil (3.43 g, 99%): ^{1}H NMR ($CDCl_3$) δ 7.4−7.6 (m, 3H), 6.8−7.0 (m, 3H), 6.4−6.6 (m, 2H), 4.5 (s, 2H), 4.2 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 152.6, 147.5, 141.7, 129.1, 117.8, 112.9, 110.2, 106.8, 41.2. This material was used for the preparation of compound **25**. Other aniline derivatives **33** prepared by this method were those used for the preparation of compounds **5**−**7**, **12**−**14**, and **18**.

3. 5-Methyl-3-[(*N*-phenylamino)methyl]isoxazole, 33 (R^1 = Ph, R^2 = CH_2-3-isoxazolyl). A solution of 5-methyl-3-(bromomethyl)isoxazole[24] (500 mg, 2.84 mmol) in acetonitrile (3 mL) under argon at ambient temperature was treated with aniline (530 mg, 5.68 mmol). After stirring overnight, precipitated solids were filtered and washed with acetonitrile. The concentrated filtrate was flash chromatographed on silica gel (ethyl acetate/hexane, 1:4) to give the desired product (411 mg, 75%). This material was used in the next step (for **29**) without further purification. The aniline derivative (R^1 = Ph, R^2 = $CH_2CH_2SO_2Me$) for **21** was prepared in an analogous manner from aniline and 2-chloroethyl methyl sulfide followed by oxidation (3-chloroperoxybenzoic acid) to the sulfone.

4. Aniline Derivative 33 (R^1 = Ph, R^2 = $CH_2(CH_2)_2$-COOEt) for the Preparaion of Compound 11. A mixture of 1-phenyl-2-pyrrolidinone (4.00 g, 25.0 mmol), absolute ethanol (20 mL) ,and concentrated hydrochloric acid (2 mL) was refluxed for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue, diluted with ethyl acetate, was washed with 5% sodium bicarbonate, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The desired product was separated from the starting material by flash chromatography on silica gel (hexanes/EtOAc, 1:1) to give a colorless solid (0.51 g, 10%): mp 40−42 °C.

5. Aniline Derivative 33 (R^1 = Ph, R^2 = NHCOOEt) for the Preparaion of Compound 24. A solution of phenylhydrazine (5.00 g, 46.24 mmol) in chloroform (40 mL) and triethylamine (7.1 mL, 50.9 mmol) was cooled to −10 °C and treated dropwise with ethyl chloroformate (4.4 mL, 46.24 mmol). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stirred for 30 min. The solvent was removed, and the residue was partitioned between ethyl acetate (150 mL) and water (60 mL). The organic layer was washed with saturated ammonium chloride solution, water, and brine and dried over sodium sulfate. The solvent was removed, and the residue was triturated with hexanes/dichloromethane to give an off-white solid (4.059 g, 49%) which was used in the next reaction without further purification.

The aniline derivative **33** (R^1 = Ph, R^2 = $CH_2PO(OEt)_2$) used for the preparation of **20** was prepared according to literature methods.[25] Compound **33** (R^1 = Ph, R^2 = CH_2CN) used for the preparation of analog **19** is commercially available.

***trans*-[(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)phenylamino]acetic Acid (9).** A solution of compound **5** (310 mg, 0.81 mmol) in THF (7 mL) and water (5 mL) at 0−5 °C was treated with 1 M lithium hydroxide (1 mL) and stirred for 3 h as the temperature rose to ambient. The mixture was diluted with ethyl acetate and extracted with water. The combined aqueous fractions were acidified with 10% citric acid to pH 3 and extracted with ethyl acetate. The organic fraction was washed with water and brine, dried (anhydrous magnesium sulfate), and concentrated to give the product as a foam. Trituration with hexanes−ether afforded the desired product (230 mg, 80%): ^{1}H NMR (DMSO-d_6/CD_3OD, 100 °C) δ 7.66 (s, 1H), 7.52 (dd, J = 1.3, 8.5 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.60−6.67 (m, 3H), 4.83 (d, J = 10.2 Hz, 1H), 4.05 (s, 2H), 3.92 (d, J = 9.8 Hz, 1H), 1.46 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.5, 134.6, 133.1, 131.0, 123.3, 120.8, 120.2, 119.4, 114.2, 114.2, 105.3, 81.6, 68.6, 59.9, 49.0, 28.4, 20.6.

(3*R*)-*trans*-[(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)(4-methyl-2-thiazolyl)amino]acetic Acid, Ethyl Ester (15). A. Compound 35. A solution of **32**[12] (810 mg, 4.0 mmol), 2-amino-4-methylthiazole (1.05 g, 9.2 mmol), and magnesium perchlorate (1.15 g, 5.1 mmol) in acetonitrile (1 mL) under argon was stirred at room temperature for 18 h. The resultant syrup was diluted with ethyl acetate (15 mL) and poured into saturated ammonium chloride solution. The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash

chromatography on silica gel (ethyl acetate/hexanes, 1:2) to give **35** as a white solid (730 mg, 58%): ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.62 (s, 3H), 2.30 (s, 3H), 3.90 (d, J = 8.8 Hz, 1H), 4.93 (d, J = 8.8 Hz, 1H), 5.40 (br s, 1H), 6.19 (s, 1H), 7.0 (d, J = 8.8 Hz, 1H), 7.58 (dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 169.01, 157.17, 147.24, 133.38, 132.58, 122.82, 118.80, 104.15, 102.60, 80.46, 75.99, 55.89, 26.46, 18.40, 16.99.

B. (3*R*)-*trans*-[(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)(4-methyl-2-thiazolyl)-amino]acetic Acid, Ethyl Ester (15). A solution of compound **35** (620 mg, 2.0 mmol) and ethyl bromoacetate (0.24 mL, 2.15 mmol) in DMF (4 mL) was treated with finely powdered K_2CO_3 (300 mg, 2.17 mmol). The reaction mixture was stirred at room temperature overnight, poured into saturated $NaHCO_3$ (10 mL), and extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 4:1) to give a colorless solid (110 mg, 14%): ^{1}H NMR ($CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 1H), 7.46 (s, 1H), 7.00 (d, J = 8.2 Hz, 1H), 6.27 (s, 1H), 5.20 (d, J = 10 Hz, 1H), 4.97 (br s, 1H), 4.20−4.50 (m, 3H), 3.70 (d, J = 10 Hz, 1H), 3.65 (d, J = 12.3 Hz, 1H), 2.35 (s, 3H), 1.67 (s, 3H), 1.43 (s, 3H), 1.40 (t, 3H).

(3*R*)-*trans*-[(2-Benzoxazolyl)(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)amino]acetic Acid, Ethyl Ester (16). A. Compound 36. To a solution of epoxide **32**[12] (2.5 g, 12.4 mmol) in THF (5 mL) was added ammonium hydroxide solution (2 mL), and the reaction mixture was heated at 75 °C in a sealed tube for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue in ethyl acetate was washed with brine and dried over Na_2SO_4. The solvent was evaporated to give an oil (2.6 g) which was used for the next step without further purification.

B. Compound 38. A solution of **36** (2.6 g, 11.9 mmol) and ethyl glyoxylate (2.5 g, 24.0 mmol) in methanol (30 mL) and acetic acid (2 mL) at 0 °C under argon was treated with $NaBH_3CN$ (1.5 g, 23.8 mmol). The reaction mixture was stirred at 0 °C for 30 min and poured into saturated sodium bicabonate solution (150 mL). The aqueous solution was extracted with ethyl acetate, and the combined organic extracts were dried over Na_2SO_4. The solvent was removed, and the residue was purified by flash chromatography on silica gel (ethyl acetate/hexanes, 3:1) to give a colorless solid (1.8 g, 48%): ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.35 (m, 2H), 3.90 (d, J = 10 Hz, 1H), 3.57 (d, J = 14 Hz, 2H), 3.54 (d, J =10 Hz, 1H), 1.64 (3, 3H), 1.40 (t, J = 7 Hz, 3H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 175.02, 157.49, 132.58, 132.23, 124.00, 119.30, 118.18, 103.58, 79.76, 71.41, 61.59, 56.93, 46.07, 26.92, 18.95, 13.99.

C. (3*R*)-*trans*-[(2-Benzoxazolyl)(6-cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)amino]acetic Acid, Ethyl Ester (16). To a solution of compound **37** (500 mg, 1.64 mmol) in DMF (5 mL) at 0 °C under argon was added NaH (60% in oil, 165 mg, 4.1 mmol). The suspension was stirred at 0 °C for 15 min, and 2-chlorobenzoxazole (230 μL, 2.1 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min and poured into saturated NH_4Cl (10 mL) and ethyl acetate (100 mL). The organic layer was separated, and the aqueous solution was extracted with ethyl acetate. The combined extracts were treated with acetic acid (0.5 mL) and stirred at room temperature for 16 h. The solution was washed with sodium bicarbonate and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography (hexane/ethyl acetate, 4:1) to give a foam (320 mg, 46%): ^{1}H NMR ($CDCl_3$) δ 7.58 (m, 3H), 7.47 (d, J = 8.2 Hz, 1H), 7.35 (t, J =7.6, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 5.72 (d, J = 10.0 Hz, 1H), 4.86 (d, J = 3.5 Hz, 1H), 4.63 (d, J = 18 Hz, 1H), 4.45 (m, 2H), 3.70 (m, 2H), 1.72 (s, 3H), 1.55 (s, 3H), 1.46 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.83, 162.41, 157.89, 148.96, 142.42, 133.50, 131.61, 124.37, 121.52, 120.43, 118.81, 118.67, 117.11, 109.25, 104.30, 80.43, 70.15, 62.66, 58.94, 45.78, 26.98, 19.20, 13.96.

(3*R*)-*trans*-2-[*N*-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)phenylamino]-*N*-ethylacetamide (17). A mixture of **6** (260 mg, 0.68 mmol) in methanol (1 mL) was treated with 70% aqueous ethylamine (1 mL, 15 mmol). After stirring at room temperature for 72 h, volatiles were removed and the residue was dissolved in ethyl acetate. The solution was washed with dilute sodium bicarbonate, water, and brine. The dried (anhydrous magnesium sulfate) organic fraction was concentrated to give an oil. Flash chromatography on silica gel (ethyl acetate/hexanes, 2:3) gave a colorless residue which was triturated with hexanes to afford the desired product (180 mg, 70%): ^{1}H NMR (DMSO-d_6, 110 °C) δ 8.02 (s, 1H), 7.55 (d, J = 9.6 Hz, 1H), 7.40 (s, 1H), 7.17 (t, J = 7.9 Hz, 2H), 6.96 (d, J = 8.6 Hz, 1H), 6.65−6.75 (m, 3H), 6.13 (s, 1H), 4.89 (d, J = 10.2 Hz, 1H), 3.95−4.00 (m, 1H), 3.80−3.84 (m, 2H), 3.16−3.21 (m, 2H), 1.50 (s, 3H), 1.32 (s, 3H), 1.07 (t, J = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.1, 133.5, 130.1, 123.4, 119.7, 119.5, 119.0, 113.6, 104.1, 81.2, 71.2, 59.5, 50.3, 35.3, 27.8, 20.0, 15.2.

(3*R*)-*trans*-4-[[2-(Acetylamino)ethyl]phenylamino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (22). A. (3*R*)-*trans*-4-[*N*-(2-Aminoethyl)phenylamino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (40). To a solution of compound **39** (4.50 g, 10.69 mmol), prepared in 67% yield from **32** by the same procedure as described for **41**, in ethanol (100 mL) at room temperature was added a mixture of methylhydrazine (50 mL) and ethanol (50 mL). The reaction was stirred at room temperature for 1.5 h and heated at reflux for 1 h. The volatiles were removed, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase was washed with brine, dried over magnesium sulfate, and evaporated to obtain an off-white foam (3.57 g, 100%): ^{1}H NMR ($CDCl_3$) δ 7.44 (dd, J = 1.75, 8.79 Hz, 1H), 7.30−7.26 (m, 4H), 6.94 (m, 4H), 4.80 (d, J = 10.55 Hz, 1H), 4.13 (d, J = 9.38 Hz, 1H), 3.78 (m, 2H), 3.34 (m, 2H), 1.52 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.46, 145.62, 133.56, 131.77, 130.19, 122.70, 121.15, 121.44, 119.28, 118.61, 116.91, 116.80, 112.71, 108.51, 103.18, 80.52, 71.13, 62.35, 44.50, 38.04, 26.35, 18.46.

B. (3*R*)-*trans*-4-[[2-(Acetylamino)ethyl]phenylamino]-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-6-carbonitrile (22). To a solution of **40** (0.5 g, 1.48 mmol) in methylene chloride (5 mL) containing pyridine (0.18 g) at 0 °C was added acetyl chloride (0.12 g, 1.55 mmol). The reaction mixture was stirred at 0 °C for 30 min followed by 2 h at room temperature. The reaction mixture was partitioned between 1 N hydrochloric acid and ethyl acetate. The organic phase was washed with saturated sodium bicarbonate solution and brine and dried over magnesium sulfate. The solvent was evaporated, and the residue was triturated with isopropyl ether to obtain the desired product (0.48 g, 85%) as a white solid: ^{1}H NMR (DMSO-d_6, 100 °C) δ 7.74 (br s, 1H), 7.66 (dd, J = 1.76, 8.80 Hz, 1H), 7.45 (s, 1H), 7.32 (m, 2H), 7.08 (m, 3H), 6.84 (m, 1H), 4.91 (d, J = 9.38 Hz, 1H), 4.05 (d, J = 9.97 Hz, 1H), 3.44−3.15 (m, 4H), 1.92 (s, 3H), 1.63 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.53, 157.21, 132.69, 131.86, 129.03, 124.73, 119.08, 118.30, 116.89, 113.74, 102.81, 80.98, 69.35 (broad), 59.75 (broad), 44.40 (broad), 36.90, 26.95, 22.54, 18.70.

(3*R*)-*trans*-[*N*-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)-*N*-(4-fluorophenyl)amino]-oxoacetic Acid, Ethyl Ester (23). A. Compound 41. The reaction mixture containing 4-fluoroaniline (1.8 g, 16.4 mmol), epoxide **32**[13] (3.0 g, 14.9 mmol), and magnesium perchlorate (3.3 g, 14.9 mmol) in acetonitrile (3 mL) was allowed to stand at room temperature for 48 h. The reaction mixture was diluted with ethyl acetate and washed with water. It was dried (magnesium sulfate) and concentrated, and the residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 7:3) to give an oil (3.8 g, 82%): ^{1}H NMR ($CDCl_3$) δ 7.57 (s, 1H), 7.40 (dd, J = 1.8, 8.2 Hz, 1H), 6.8−6.95 (m, 3H), 6.65 (m, 2H), 4.40 (t, J = 9.4, 8.8 Hz, 1H), 3.80 (d, J = 9.4 Hz, 1H), 3.66 (d, J = 9.4 Hz, 1H), 2.76 (s, 1H), 1.53, 1.33 (s, 3 H each); ^{13}C NMR ($CDCl_3$) 158.3, 156.5, 154.7, 143.4, 132.9, 132.3, 124.8, 119.0, 118.3, 116.4, 116.0, 115.8, 115.4, 114.8, 114.7, 103.9, 79.8, 73.5, 54.6, 26.6, 19.3.

B. Compound 42. A solution of **41** (1.0 g, 3.2 mmol) in dimethylformamide (5 mL) under argon at 0 °C was treated with sodium hydride (0.3 g, 6.4 mmol, 60% oil dispersion) and stirred for 10 min. The reaction mixture was treated with 4-methoxybenzyl chloride (550 mg, 3.5 mmol) and stirred at room temperature for 1 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate, and the combined extracts were washed with water and brine. After drying over anhydrous magnesium sulfate, the solvent was removed to give the desired product (1.3 g, 94%) as an oil. This material was subjected to the next reaction without further purification.

C. Compound 43. The reaction mixture containing **42** (0.5 g, 1.1 mmol) in acetonitrile (2 mL) was treated with ethyl oxalyl chloride (0.19 g, 1.4 mmol) followed by 4-(dimethylamino)pyridine (20 mg). The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl acetate, and washed with 10% hydrochloric acid, sodium bicarbonate solution, and brine. After drying over anhydrous magnesium sulfate, the solvent was removed to give an oil which was used in the next step without purification.

D. (3*R*)-*trans*-[*N*-(6-Cyano-3,4-dihydro-3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran-4-yl)-*N*-(4-fluorophenyl)amino]oxoacetic Acid, Ethyl Ester (23). To a solution of **43** (0.5 g, 0.88 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (2 mL), and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated, and the residue in ethyl acetate was washed with saturated sodium bicarbonate solution, water, and brine. After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 1:1) to give an oil (0.2 g, 55%). Trituration with hexanes−ether provided the desired product as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.61 (s, 1H), 7.43 (dd, J = 1.0, 8.2 Hz, 1H), 7.10−6.92 (m, 4H), 6.80 (d, J = 8.2 Hz, 1H), 5.67 (s, 1H), 3.98 (m, 2H), 3.52 (m, 2H), 1.38, 1.22 (s, 3H each); ^{13}C NMR ($CDCl_3$) 165.0, 162.7, 158.1, 134.3, 133.1, 132.3, 132.1, 122.2, 119.9, 117.6, 117.3, 105.4, 81.1, 70.5, 63.1, 27.3, 19.4, 14.5.

(3*R*)-*trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-[*N*-[(3-methyl-1,2,4-oxadiazol-5-yl)methyl]phenylamino]-2*H*-1-benzopyran-6-carbonitrile (26). A solution of *N*-hydroxyacetamidine (0.16 g, 2.1 mmol) in dry tetrahydofuran (3 mL) under argon was treated with sodium hydride (50%, 0.053 g, 2.2 mmol) and 4 Å molecular sieves (1.8 g) and heated at 50 °C for 1 h. A solution of compound **6** (0.4 g, 1.0 mmol) in tetrahydrofuran (1 mL) was added, and the reaction mixture was heated at 50 °C for 4 h. The reaction mixture was cooled to ambient temperature, diluted with dichloromethane (150 mL), and washed with water. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexanes/ethyl acetate, 7:3) to give a colorless solid (0.25 g, 61%): ^{1}H NMR ($CDCl_3$) δ 7.40 (d, J = 10.0 Hz, 1H), 7.30 (s, 1H), 7.18 (m, 2H), 6.75−6.85 (m, 4H), 5.54 (d, J = 3.0 Hz, 1H), 5.03 (s, 1H), 4.65 (d, J = 18.1 Hz, 1H), 4.17 (s, 1H), 3.65 (s, 1H), 2.3 (s, 3H), 1.51 and 1.33 (s, 3H each); ^{13}C NMR ($CDCl_3$) 179.0, 166.9, 158.1, 133.3, 131.8, 129.9, 122.3, 119.6, 119.0, 118.7, 113.1, 104.1, 80.7, 70.6, 27.3, 19.5, 11.5.

(3*R*)-*trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-[*N*-(2-oxazolylmethyl)phenylamino]-2*H*-1-benzopyran-6-carbonitrile (27). A. Compound 44. A solution of **6** (1.5 g, 3.94 mmol) in 2-aminoacetaldehyde dimethyl acetal (5 mL) was heated under reflux for 16 h. The mixture was diluted with ethyl acetate (100 mL), washed with 10% citric acid and brine, and dried ($MgSO_4$). The solvent was removed, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:1) to give a white foam (1.66 g, 96%): ^{1}H NMR ($CDCl_3$, 60 °C) δ 7.43 (d, J = 7.7 Hz, 1H), 7.31−7.26 (m, 3H), 6.92−6.76 (m, 4H), 6.71 (br s, 1H), 5.03 (d, J = 9.9 Hz, 1H), 4.95 (d, J = 4.0 Hz, 1H), 4.38 (t, J = 4.0 Hz, 1H), 3.99 (d, J = 18.1 Hz, 1H), 3.84−3.63 (m, 1H), 3.54 (d, J = 18.5, 1H), 3.40 (s, 3H), 3.20 (dt, J = 14.0, 4.2 Hz, 1H), 1.55, 1.37 (s, 3H each); ^{13}C NMR ($CDCl_3$, 60 °C) 171.5, 158.2, 145.5, 133.2, 132.1, 129.3 (2C), 122.90, 119.31, 118.6, 116.6, 113.2, 104.2, 102.9, 80.6, 70.2, 58.1, 55.1, 54.9, 40.3, 26.9, 19.0.

B. (3*R*)-*trans*-3,4-Dihydro-3-hydroxy-2,2-dimethyl-4-[*N*-(2-oxazolylmethyl)phenylamino]-2*H*-1-benzopyran-6-carbonitrile (27). The reaction mixture containing **44** (610 mg, 1.40 mmol) in THF (5 mL) was treated with 6 N hydrochloric acid (5 mL) and stirred at room temperature until completion. The solution was diluted with diethyl ether (100 mL), washed with water (until the pH was 6.5−7) and brine, and dried over $MgSO_4$. The solvent was removed, and the residue was immediately dissolved in dichloromethane (5 mL) and treated with a freshly prepared solution containing triphenylphosphine (371 mg, 1.414 mmol), iodine (355 mg, 1.40 mmol), and triethylamine (0.4 mL). The dark brown reaction mixture was stirred at room temperature for 30 min, diluted with diethyl ether (50 mL), and washed with water, 5% sodium bisulfite, and brine. After drying over anhydrous $MgSO_4$, the solvent was removed to give a white foam which was purified by flash chromatography on silica gel (12% EtOAc in hexanes) to give a colorless solid (44 mg, 10%): ^{1}H NMR ($CDCl_3$, 55 °C): δ 7.66 (s, 1H), 7.45 (dd, J = 2.1, 8.4 Hz, 1H), 7.41 (s, 1H), 7.26−7.20 (m, 2H), 7.07 (s, 1H), 6.90 (d, J = 9.0 Hz, 1H), 6.84−6.80 (m, 3H), 5.10 (d, J = 9.7 Hz, 1H), 4.63 (d, J = 18.2 Hz, 1H), 4.22 (d, J = 18.2 Hz, 1H), 3.79 (d, J = 9.9 Hz, 1H), 1.6, 1.43 (s, 3H each); ^{13}C NMR ($CDCl_3$, 60 °C) 163.7, 158.1, 139.1, 132.89, 131.7, 129.5 (2C), 126.8, 123.0, 119.0, 118.8, 118.4, 113.2, 104.1, 80.7, 70.5, 59.5, 44.1, 27.2, 19.4.

Biological Assays. EC_{25} values for increasing time to contracture were determined in isolated perfused globally ischemic rat hearts. Compounds were initially evaluated at 10 μM concentration. Those demonstrating greater than 25% increase in time to the onset of contracture were subjected to concentration−response studies to determine EC_{25} values. To compare the antiischemic and peripheral vasodilator potencies, we determined IC_{50} values for relaxation of the methoxamine-contracted rat aorta. Experimental details of both methods are described.[18]

For pharmacokinetic studies, the hydrochloride salt of **3** (30 μmol/kg) was administered to male rats as a solution (total volume: 0.75 mL for both routes) in ethanol:poly(ethylene glycol)-400:water (2:3:5). Rats were dosed either intravenously (N = 4) by injection into the jugular vein or orally (N = 4) by gavage. Serial blood samples were obtained at 0, 5, 10, 20, and 40 min and at 1, 2, 4, 6, 8, 12, 24, and 28 h after dosing. Plasma was prepared from each blood sample by centrifugation and analyzed by a specific LC/MS method for compound **3**. Pharmacokinetic parameters were calculated with standard model-independent methods. Areas under the curve (AUC) were calculated using Language integration and extrapolated to infinity with the iv elimination half-life. The systemic oral bioavailability was estimated by dividing the mean $AUC_{0\rightarrow\infty}$ value for the oral doses by the mean $AUC_{0\rightarrow\infty}$ value for the intravenous doses.

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