# Cardioselective Antiischemic ATP-Sensitive Potassium Channel Openers. 4. Structure−Activity Studies on Benzopyranylcyanoguanidines: Replacement of the Benzopyran Portion

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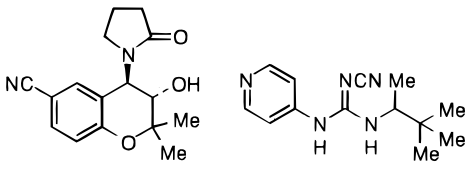
The results of our efforts aimed at the replacement of the benzopyran ring of the lead cardiac selective antiischemic ATP-sensitive potassium channel ($K_{ATP}$) opener (**4**) are described. Systematic modification of the benzopyran ring of **4** resulted in the discovery of a structurally simpler acyclic analog (**8**) with slightly lower antiischemic potency than the lead compound **4**. Further structure−activity studies on the acyclic analog **8** provided the 2-phenoxy-3-pyridylurea analog **18** with improved antiischemic potency and selectivity compared to the benzopyran-based compound **4**. These data demonstrate that the benzopyran ring of **4** and its congeners is not mandatory for antiischemic activity and cardiac selectivity. The results described in this paper also show that, as for the benzopyran class of compounds, the structure−activity relationships for the antiischemic and vasorelaxant activities of $K_{ATP}$ openers are distinct. The mechanism of action of the acyclic analogs (e.g., **18**) still appears to involve $K_{ATP}$ opening as their cardioprotective effects are abolished by pretreatment with the $K_{ATP}$ blocker glyburide.

## Introduction

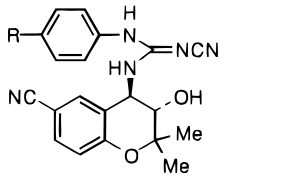
The major clinical utility of the ATP-sensitive potassium channel ($K_{ATP}$) openers (e.g., cromakalim) was originally thought to be for the treatment of hypertension, primarily due to their potent peripheral vasodilating properties.[1] However, the clinical studies with the first generation agents (e.g., **1** and **2**) have failed to demonstrate any clear advantages of these compounds over the more established antihypertensive agents such as the angiotensin-converting enzyme inhibitors and calcium channel blockers. Therefore, additional indications need to be explored for these drugs to be successful as pharmaceuticals. Although experimental studies show that the first generation agents may be effective for the treatment of a variety of diseases (asthma, urinary incontinence, ischemia, etc.) besides hypertension, their clinical utility is limited due to lack of tissue selectivity. For example, cromakalim (**1**) and pinacidil (**2**) can open $K_{ATP}$ in a variety of tissues.[2] Tissue-selective agents are desired to explore the full potential of $K_{ATP}$ openers for various indications.




Cromakalim (**1**)




Pinacidil (**2**)




**3**: BMS-180448 (R = Cl; 3S,4R)
**4**: R = H (racemate)

We have been interested in the role of $K_{ATP}$ in myocardial ischemia. Accordingly, we have shown that $K_{ATP}$ openers have direct cardioprotective properties which do not require contribution from vasodilation.[3] Although effective as cardioprotective agents when given directly into the coronary artery, the potent vasorelaxant properties of the first generation agents can compromise the tissue already at risk by causing hypotension and coronary artery steal.[4] Previous reports from our laboratories have shown that the structure−activity relationships for the antiischemic and vasorelaxant potencies of the benzopyran-based $K_{ATP}$ openers are distinct.[5] Our efforts to find cardioprotective $K_{ATP}$ openers with a lower degree of vasorelaxant potency relative to the first generation agents (i.e., cardiac selective agents) resulted in the identification of BMS-180448 (**3**).[5] We have recently published detailed structure−activity relationships on the lead compound (**4**) that led to the discovery of the clinical candidate BMS-180448 (**3**).[6,7] The results of those studies helped us understand the minimum structural requirements for the antiischemic activity of **4** and its congeners. The present publication describes our studies aimed at the replacement of the core benzopyran ring of **4** with simpler surrogates.

## Design Strategy

The objective of this work was to discover simpler molecules with a similar or improved pharmacological profile (e.g., increased potency and selectivity) compared to the lead benzopyran derivative **4**. The simpler analogs were expected to be more amenable to rapid development of structure−activity relationships for the optimization of antiischemic potency and selectivity. The design strategy beginning with the lead structure **4** is outlined in Scheme 1. We concentrated on modification of the benzopyran portion of **4** since it is the most complex area of the molecule with two adjacent chiral centers at C3 and C4. A summary of the structure−activity relationships for antiischemic activity of **4** is given in Figure 1. The cyanoguanidine moiety can be

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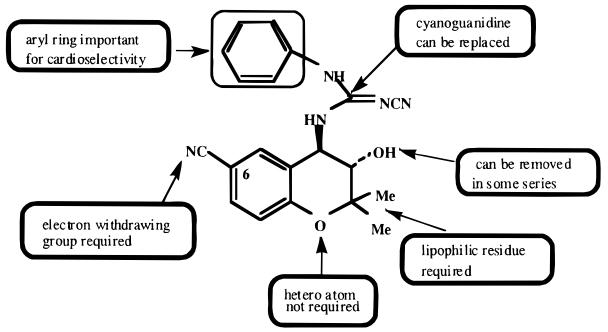
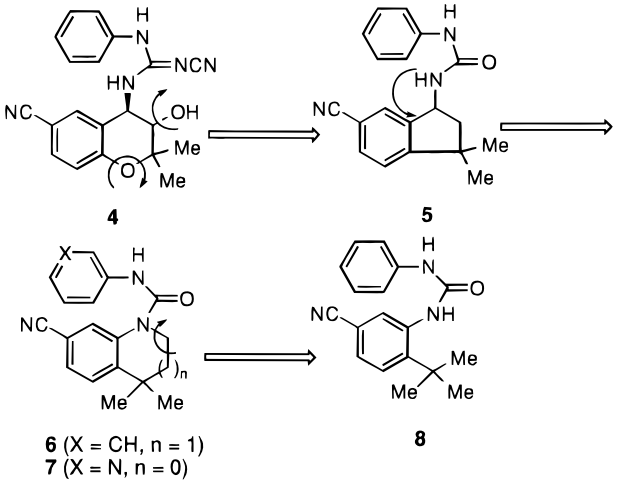



**Figure 1.** A summary of the structure−activity relationships for antiischemic potency of the lead benzopyranylcyanoguanidine **4**.

**Scheme 1**

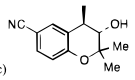
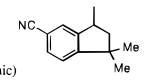
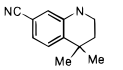
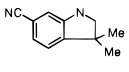
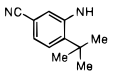



replaced with a urea.[5] Neither the benzopyran oxygen nor the C3 hydroxyl group is required for antiischemic activity of **4** (Figure 1).[6] These changes, when combined in a single molecule, provided the indan analog **5** with antiischemic potency comparable to the starting molecule **4** (Table 1).[6] The indan analog **5** contains a single chiral center compared to the two chiral centers usually present in benzopyran derivatives (e.g., **4**). Further simplification of the structure of **5** was envisioned to arise from the inclusion of the benzylic nitrogen of **5** into the indan ring (**5** → **6**) (Scheme 1). Unlike the indan analog **5**, quinoline **6** has no chiral centers. If sufficiently active, the relatively rigid framework of **6** was expected to provide the incentive to explore its simplified acyclic analogs (e.g., **8**). Compounds related to **8** are synthetically more easily accessible than the benzopyran-based compounds (**4**) for rapid development of structure−activity relationships. The successful realization of this strategy is described in this publication.

## Chemistry

The synthesis of the quinoline nucleus of **6** started with the previously described indanone **19**[8] (Scheme 2). The nitro group of **19** was reduced to the amine **20** by catalytic hydrogenation. The amine **20** was converted to the bromide **21** by a two-step process which involves conversion of **20** to the corresponding diazonium salt followed by treatment with copper(I) bromide. The ketone in **21** was converted to a mixture of oximes (**22**) under standard conditions (hydroxylamine hydrochloride, sodium acetate). Treatment of **22** with *p*-toluenesulfonyl chloride provided the tosylate **23** which upon

**Table 1.** Vasorelaxant and Antiischemic Potencies of Compounds **4**−**8**

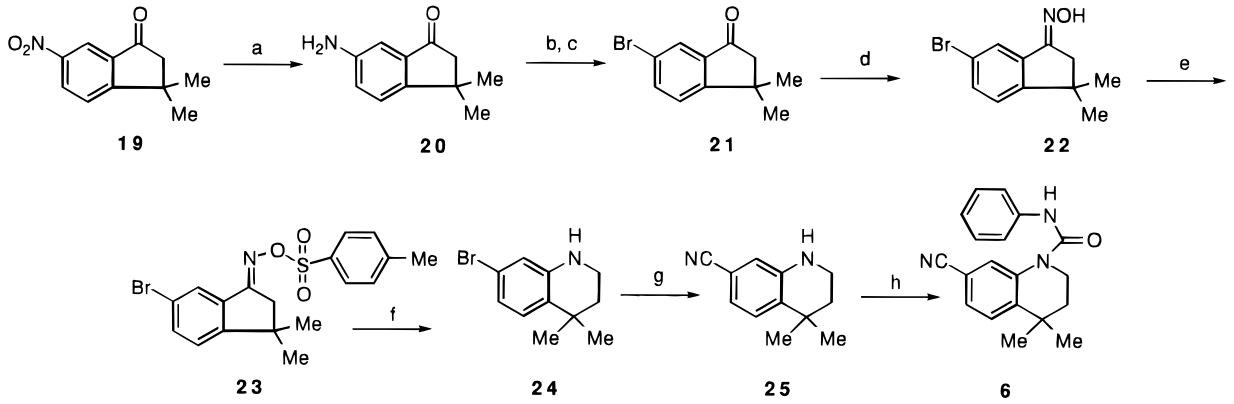
| Com'd | R | X | Y | Time to Contracture[a] $EC_{25}$, μM or % inc. @ 10μM | Vasorelaxant potencies[b] $IC_{50}$, μM (95% C. L.) | Ratio $EC_{25}/IC_{50}$ |
|---|---|---|---|---|---|---|
| **4** (racemic) |  | CH | NCN | 11.0 | 1.4 (0.98, 1.93) | 7.9[c] |
| **5** (racemic) |  | CH | O | 9.4 | 1.3 (0.67, 2.42) | 7.2[c] |
| **6** |  | CH | O | 26.0 | 6.7 (4.3, 11.0) | 3.9 |
| **7** |  | N | O | 28.3 | 1.5 (0.91, 2.2) | 18.8 |
| **8** |  | CH | O | 33.8 | 1.7 (1.1, 2.7) | 19.9 |
| **1** (cromakalim) | | | | 8.9 | 0.032 (0.021, 0.049) | 278.1 |

[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 (in minutes) necessary during total global ischemia to increase end diastolic pressure by 5 mmHg. Each value is an average of three or four determinations and is within approximately ±20%. [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.

reduction with diisobutylaluminum hydride underwent the reductive Beckmann rearrangement[9] to provide the desired quinoline **24** as a major product. A small amount of the isoquinoline which could have been formed due to migration of the alkyl group during the Beckmann rearrangement (**23** → **24**) was not isolated. The bromide in **24** was smoothly converted to the nitrile **25** by treatment with copper(I) cyanide in hot *N*-methylpyrrolidone. Replacement of the nitro group in **19** with a bromine **21** was necessitated due to the failure of the Beckmann rearrangement in the presence of a nitro group. The phenylurea analog **6** was prepared by treatment of **25** with phenyl isocyanate.

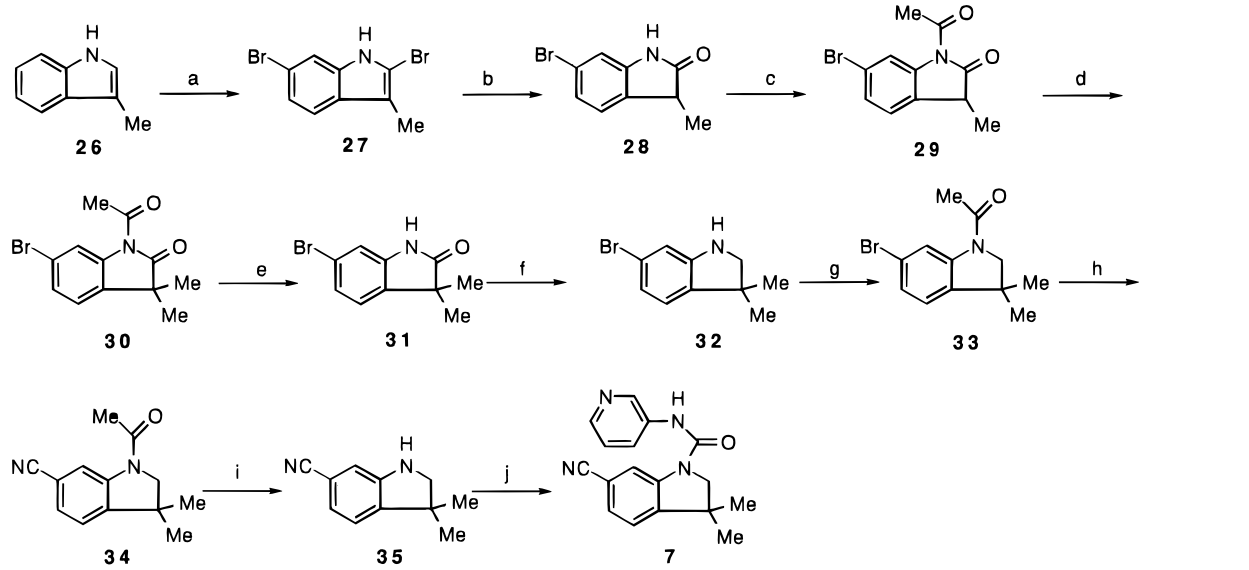
The synthesis of the dihydroindole analog **7** is summarized in Scheme 3. The starting lactam **28** was prepared from 3-methylindole (**26**) via the dibromide **27**.[10a] The nitrogen of the lactam (**28**) was protected as an acetate (**29**), and the second methyl group (**30**) was introduced by alkylation with methyl iodide in the presence of sodium hydride.[10b] We were unable to accomplish C-methylation of **28** without prior protection of the lactam nitrogen. Saponification of the acetate in **30** followed by reduction of **31** with sodium bis(2-methoxyethoxy)aluminum hydride gave the dihydroindole **32** in good yield. Attempts to replace the bromine in **32** with a nitrile failed, partly due to the susceptibility of **32** to oxidation under forcing conditions. Thus, the amine in **32** had to be reprotected as an acetate (**33**) before replacement of the bromine with a cyano group (**34**). Deprotection of **34** to **35** was carried out in 91% yield by heating **34** with aqueous hydrochloric acid. The 3-pyridylurea (**7**) was formed from **35** by heating with

**Scheme 2**[a]



[a] Reagents: (a) 5% Pd−C, methanol, $H_2$, 15 psi, 100%; (b) EtOH, 48% HBr, $NaNO_2$, 0 °C; (c) CuBr, 48% HBr, 95 °C, 79% from **20**; (d) $NH_2OH$·HCl, NaOAc, EtOH, heat, 100%; (e) *p*-toluenesulfonyl chloride, pyridine, 99%; (f) diisobutylaluminum hydride, $CH_2Cl_2$, −78 to 0 °C, 49%; (g) CuCN, *N*-methylpyrrolidone, 185−190 °C, 53%; (h) phenyl isocyanate, 4-(dimethylamino)pyridine, acetonitrile, heat, 83%.

**Scheme 3**[a]



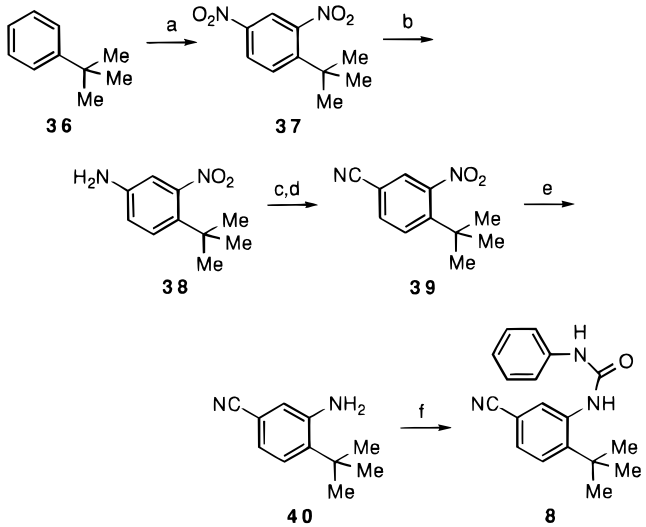
[a] Reagents: (a) *N*-bromophthalimide, benzene, 51%; (b) $H_2SO_4$, dioxane, 98%; (c) $Ac_2O$, xylene, reflux, 78%; (d) NaH, MeI, THF, 100%; (e) NaOH, EtOH, 98%; (f) sodium bis(2-methoxyethoxy)aluminum hydride, toluene, 85 °C, 73%; (g) AcCl, triethylamine, $CH_2Cl_2$, 99%; (h) CuCN, *N*-methylpyrrolidone, 83%; (i) 5 N HCl, 91%; (j) nicotinyl azide, toluene, 85 °C, 80%.

nicotinyl azide in toluene. The mild basicity of the amine in **35** obviates the need for the prior formation of 3-pyridyl isocyanate from nicotinoyl azide.

For the preparation of acyclic urea analog **8**, *tert*-butylbenzene **36** was converted to the amino compound **38** by the published procedure (Scheme 4).[11] The less hindered nitro group of **37** was selectively reduced to compound **38** (86%) with sodium sulfide−sulfur mixture. The amino group in **38** was changed to a nitrile (**39**) via the diazonium salt, prepared from **38** by treatment with sodium nitrite in hydrochloric acid. The nitro group of **39** was reduced with stannous chloride and the corresponding amine **40** was converted to the phenylurea **8** by treatment with phenyl isocyanate.

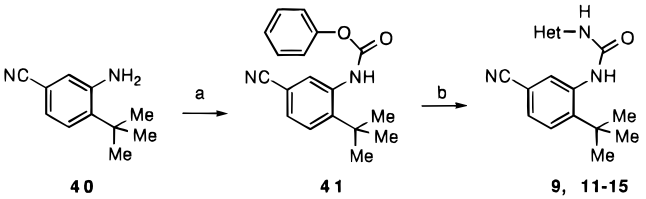
The additional urea analogs (**9**, **11**−**15**) of **8** were prepared from the amine **40** via the phenyl carbamate **41**, readily obtained by treatment of **40** with phenyl chloroformate in pyridine (94%). The phenyl carbamate **41** on heating with the appropriate amines provided the desired products in good yields (Scheme 5). The cyanoguanidine analog **10** of **9** was prepared from the amine **40** via the phenoxy intermediate **42** by the published procedure (Scheme 6).[7]

**Scheme 4**[a]



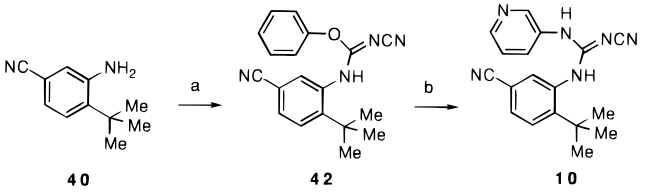
[a] Reagents: (a) $H_2SO_4$, $HNO_3$, 70%; (b) water, sodium sulfide−sulfur, 86%; (c) HCl, $NaNO_2$; (d) CuCN, KCN, water, 42% from **38**; (e) stannous chloride, ethanol, 100%; (f) phenyl isocyanate, heat, 86%.

**Scheme 5**[a]



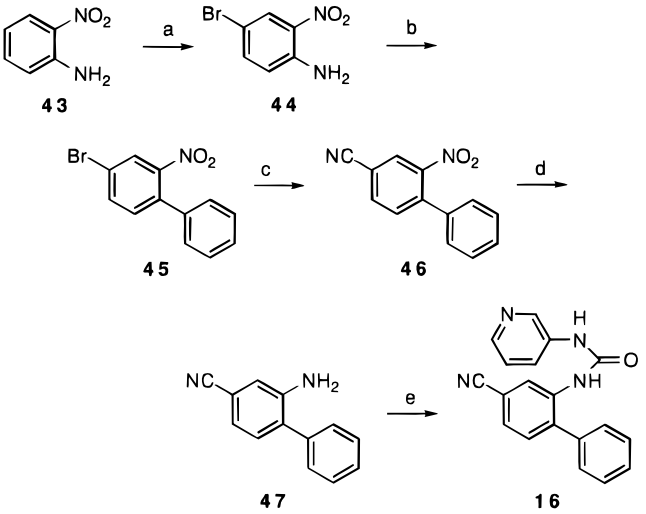

[a] Reagents: (a) pyridine, phenyl chloroformate, 94%; (b) Het-$NH_2$, DMF, 4-(dimethylamino)pyridine, heat.

**Scheme 6**[a]




[a] Reagents: (a) NaH, THF, diphenyl cyanocarbonimidate, 77%; (b) 3-aminopyridine, DMF, 100 °C, 58%.

**Scheme 7**[a]




[a] Reagents: (a) AcOH, $Br_2$, 68%; (b) AcOH, sodium nitrite then NaOAc, benzene, 38%; (c) Cu(I)CN, *N*-methylpyrrolidone, 180 °C, 56%; (d) stannous chloride dihydrate, EtOH, 89%; (e) nicotinyl azide, toluene, heat, 73%.

The synthesis of the biphenyl analog **16** is outlined in Scheme 7. The biphenyl intermediate **45** was prepared from 2-nitroaniline (**43**) by the literature procedure.[12] The bromine in **45** was replaced with a nitrile (**46**) by heating **45** with copper(I) cyanide in hot *N*-methylpyrrolidone. Reduction of the nitro group in **46** and derivatization of the resulting amine **47** by the standard procedure provided the desired 3-pyridylurea **16**.

The sulfonamide analog **17** was prepared from 4-amino-3-nitrobenzonitrile (**48**) in a straightforward manner (Scheme 8). The sulfonamide **49** was prepared in a low yield (16%) by successive treatment of **48** with sodium hydride and *p*-toluenesulfonyl chloride in dimethyl sulfoxide. The nitro group (**49**) was reduced with stannous chloride, and the resulting amine (**50**) was converted to the 3-pyridylurea analog **19** under standard conditions (nicotinoyl azide, toluene, heat).

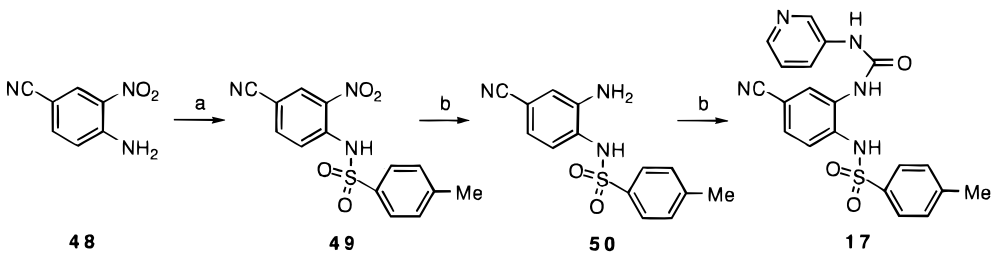
The synthesis of the phenoxy analog **18** is summarized in Scheme 9. The phenoxy group (**52**) was introduced by heating 4-chloro-3-nitrobenzonitrile (**51**) with phenol in the presence of potassium carbonate. Reduction of the nitro group of **52** with stannous chloride followed by treatment of the resulting amine **53** with nicotinoyl azide in hot toluene furnished the desired product (**18**) in 62% overall yield from **52**.

## 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.[13] 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.[14] 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.[14] Contracture develops due to rigor bond formation, presumably due to lack 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. Validity of these *in vitro* test systems to predict antiischemic selectivity *in vivo* has been previously demonstrated by detailed studies with BMS-180448 (**3**).[15]

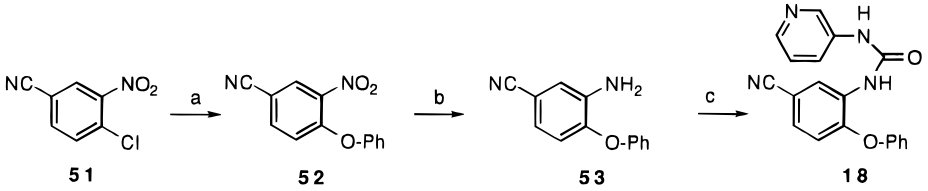
For initial studies, some analogs (e.g., **7**) had to be evaluated as pyridylureas because of poor aqueous solubilities of the corresponding phenylureas. The higher aqueous solubility of pyridylurea analogs is presumably due to a combination of factors which include solvation, hydrogen-bonding capability, and the potential for protonation. Previous studies have shown that the 3-pyridylurea and phenylurea analogs of **4** have comparable antiischemic potencies.[7] The cyano group, usually present at C6 of the benzopyran-based compounds (e.g., **4**), was kept constant throughout these studies. As shown in Table 1, the quinoline analog **6** is about 2-fold less active as an antiischemic agent compared to the corresponding benzopyran and indan derivatives, **4** and **5**, respectively. By virtue of having lower vasorelaxant potency relative to **4** and **5**, the quinoline derivative **6** shows slightly improved cardiac selectivity over **4** and **5.** The indoline analog **7** offered

**Scheme 8**[a]



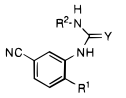

[a] Reagents: (a) NaH, DMSO, *p*-toluenesulfonyl chloride, 16%; (b) stannous chloride dihydrate, EtOAc, 84%; (c) nicotinyl azide, toluene, heat, 75%.

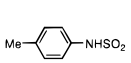
**Scheme 9**[a]




[a] Reagents: (a)PhOH, $K_2CO_3$, DMF, 63%; (b) $SnCl_2$, EtOAc, 88%; (c) nicotinyl azide, toluene, 95 °C, 70%.

**Table 2.** Vasorelaxant and Antiischemic Potencies of Biaryl Urea 8 and Its Analogs




| Com'd | $R^1$ | $R^2$ | Y | Time to Contracture[a] $EC_{25}$, μM or % inc. @ 10μM | Vasorelaxant potencies[b] $IC_{50}$, μM (95% C. L.) | Ratio $EC_{25}/IC_{50}$ |
|---|---|---|---|---|---|---|
| 8 |  |  | O | 33.8 | 1.7 (1.1, 2.7) | 19.9 |
| 9 |  |  | O | 29.7 (25%) | 25.7 (17.2, 38.3) | 1.2 |
| 10 |  |  | NCN | 16% | 1.2 (0.63, 2.3) | |
| 11 |  |  | O | 25% | 25.7 (17.2, 38.3) | |
| 12 |  |  | O | 14% | 7.8 (5.0, 12.0) | |
| 13 |  |  | O | 2% | 12.4 (9.5, 16.1) | |
| 14 |  |  | O | 11.9 | 15.3 (12.7, 18.3) | 0.77 |
| 15 |  |  | O | 19.2 | 1.6 (1.2, 2.2) | 12.0 |
| 16 |  |  | O | 12% | 22.8 (16.5, 31.6) | |
| 17 |  |  | O | 0% | >100 | |
| 18 |  |  | O | 2.0 | 1.0 (0.81, 1.26) | 2.0 |

[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 (in minutes) necessary during total global ischemia to increase end diastolic pressure by 5 mmHg. Each value is an average of three or four determinations and is within approximately ±20%. [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.

no improvement in the antiischemic potency of **6**. At this stage, we were far from meeting our objective, as the syntheses of **6** and **7** were much more complicated than those of the benzopyran-based analogs (e.g., **4**).[5−7] Further structural simplification was achieved by the carbon−nitrogen bond scission in **6** (Scheme 1). The resulting acyclic urea **8** has antiischemic potency comparable to **6** (Table 1). Although slightly less potent than the benzopyran analog **4**, the structural simplicity of **8** made it attractive for further structure−activity work. The results of those studies are summarized in Table 2.

As expected, the 3-pyridylurea analog **9** of **8** has antiischemic potency comparable to **8**. Since the pyridylurea analogs show better aqueous solubilities than the corresponding phenylurea derivatives, further work was concentrated on the heterocyclic analogs of **8**. The cyanoguanidine analog **10** offers no improvement over the corresponding urea **9**. Although the 2-pyridylurea analog **11** has antiischemic potency similar to **9**, the 4-pyridylurea (**12**) appears to be less potent than **9**. Introduction of an additional nitrogen atom into the pyridine ring of **9** has a variable effect on antiischemic potency. While the pyrimidine analog **13** has a reduced antiischemic potency relative to that of **9**, the pyrazine derivative **14** shows a slight improvement in antiischemic potency over **9**. Substitution of the pyridine ring of **9** with a chlorine atom (**15**) is slightly beneficial to both antiischemic and vasorelaxant potencies. The changes on the pyridine ring of **9** indicate that, although some qualitative trends in structure-activity relationships can be noted, the antiischemic potency of **9** largely remains constant. These observations are similar to those previously reported for the arylurea portion of the benzopyran-based antiischemic $K_{ATP}$ openers (e.g., **4**).[7]

We have previously reported that the antiischemic potency of the benzopyran-based $K_{ATP}$ openers (e.g., **4**) is extremely sensitive to the presence of a *gem*-dimethyl group at C2 of the benzopyran ring.[6] Assuming that compounds **4** and **9** are expressing their biological effects by binding in a similar manner, we expected a more profound effect of changes to the *tert*-butyl group of **9**. As it turned out, replacement of the *tert*-butyl group of **9** with a more rigid phenyl group (**16**) has a deleterious effect on antiischemic potency. Increasing the distance between the two phenyl groups of **16** via a sulfonamide linker (**17**) causes complete abolition of antiischemic potency. The best compound of this series was obtained by inserting an oxygen atom (**18**) between the phenyl rings of compound **16**. Compound **18** shows a 5-fold improvement in antiischemic potency over the starting benzopyran **4**. Further, the phenoxy analog **18** shows slightly improved cardiac selectivity relative to **4**. Comparison among **9** and **16**−**18** indicates that the size of the lipophilic substituent is important for antiischemic potency. The *tert*-butyl and phenyl groups of **9** and **16**, respectively, may not be able to access the presumed lipophilic pocket occupied by the *gem*-dimethyl group of the benzopyran series of compounds (**4**). Whatever the reasons, these results indicate that the antiischemic potency of the acyclic analogs (e.g., **8**) is most sensitive to changes at the group that mimics the *gem*-dimethyl group at C2 of the benzopyran-based compounds (e.g., **4**).

As shown by the comparison of ratios between antiischemic and vasorelaxant potencies, the most potent compound (**18**, $EC_{25} = 2\ \mu M$) of this series is over 100-fold more cardiac selective than the reference agent cromakalim ($EC_{25} = 9.8\ \mu M$). Thus, in addition to having a simplified structure, compound **18** shows an improved pharmacological profile compared to the benzopyran-based compounds (e.g., cromakalim). Further, it offers the opportunity to explore structure−activity

**Table 3.** Physical Properties of Compounds **6**−**18**

| compd | molecular formula | microanalysis | physical characterization | mp (°C)[a] |
|---|---|---|---|---|
| **4** | see ref 6 | | | |
| **5** | see ref 6 | | | |
| **6** | $C_{19}H_{19}N_3O$ | C, H, N | off-white solid | 174−5 (A) |
| **7** | $C_{17}H_{16}N_4O$ | C, H, N | white solid | 220−2 (B) |
| **8** | $C_{18}H_{19}N_3O{\cdot}0.19H_2O$ | C, H, N | off-white solid | 225−6 (C) |
| **9** | $C_{17}H_{18}N_4O{\cdot}0.43H_2O$ | C, H, N | off-white solid | 194−6 (D) |
| **10** | $C_{18}H_{18}N_6{\cdot}0.3C_3H_8O$ | C, H, N | off-white solid | 219−21 (C) |
| **11** | $C_{17}H_{18}N_4O{\cdot}0.2$EtOAc | C, H, N | off-white solid | 198−200 (B) |
| **12** | $C_{17}H_{18}N_4O{\cdot}1.2H_2O$ | C, H, N | amorphous solid | 125−30 (B) |
| **13** | $C_{16}H_{17}N_5O$ | C, H, N | colorless solid | 208−9 (B) |
| **14** | $C_{16}H_{17}N_5O{\cdot}0.02H_2O$ | C, H, N | colorless solid | 203−5 (B) |
| **15** | $C_{17}H_{17}ClN_4O{\cdot}0.12H_2O$ | C, H, N | colorless solid | 233−4 (B) |
| **16** | $C_{19}H_{14}N_4O{\cdot}0.07H_2O$ | C, H, N | off-white solid | 180−2 (C) |
| **17** | $C_{20}H_{17}N_4O_3S{\cdot}0.11H_2O$ | C, H, N | colorless powder | 221−3 (E) |
| **18** | $C_{19}H_{14}N_4O_2{\cdot}0.09H_2O$ | C, H, N | colorless solid | 208−9 (F) |

[a] Solvent for crystallization: A, trituration with isopropyl ether; B, unrecrystallized material; C, 2-propanol; D, EtOAc/2-propanol/hexanes; E, DMF/EtOAC/hexanes; F, EtOAc/MeOH/hexanes.

relationships for the discovery of $K_{ATP}$ openers with improved antiischemic potency and cardiac selectivity.

The cardiac selectivity, as determined by the ratio of vasorelaxant and antiischemic potencies, varies 25-fold (Table 2). These data support our earlier results, demonstrating that, regardless of the structural class, the structure−activity relationships for antiischemic and vasorelaxant activities of $K_{ATP}$ openers are distinct. We have no clear explanation for these differences at the present time other than the hypothesis that the antiischemic and vasorelaxant actions of $K_{ATP}$ openers may be mediated via different receptor subtypes. To ensure that the mechanism of antiischemic activity of **8** and its derivatives is similar to that of the benzopyran-based compounds, we studied the effect of the $K_{ATP}$ blocker glyburide on the cardioprotective actions of the most potent compound **18** of this series. This is especially important since minor changes in the structure of the benzopyran-based $K_{ATP}$ openers can have a dramatic effect on their mechanism of action.[16] Previous studies have shown that the cardioprotective effects of structurally different $K_{ATP}$ openers are abolished by pretreatment with glyburide.[14,17] Glyburide is relatively selective in abolishing the cardioprotective effects of $K_{ATP}$ openers as it has no effect on the cardioprotective actions of agents working via other mechanisms.[18]

The effect of glyburide (0.3 $\mu$M) on the increase in time to contracture induced by 10 $\mu$M of **18** in isolated globally perfused rat hearts is shown in Figure 2. This concentration of glyburide has been shown to be without an effect on the time to contracture in the isolated perfused rat hearts.[14,17] Compound **18** was given in the perfusion medium 10 min prior to the onset of total global ischemia. The development of contracture is measured as the time necessary to increase end diastolic pressure by 5 mmHg compared to baseline value.[14] The pyridylurea analog **18** (10 $\mu$M) caused a significant increase in the time (22 min) to the onset of contracture compared to the vehicle-controlled hearts (17 min). This increase in time to contracture was completely abolished by pretreatment with glyburide (0.3 $\mu$M), indicating that the cardioprotective effects of **18** are in some fashion related to the opening of $K_{ATP}$ in the myocardium. Further, the combination of glyburide (0.3 $\mu$M) and compound **18** (10 $\mu$M) was found to be proischemic as shown by a decrease (30%) in the time to the onset of contracture compared to the vehicle-treated hearts. This proischemic effect of glyburide in combination with a $K_{ATP}$ opener previously has been shown for several structurally different $K_{ATP}$ openers.[14,17] These data are consistent with the profile of antiischemic activity of **18** being similar to that of other $K_{ATP}$ openers.[5−7]

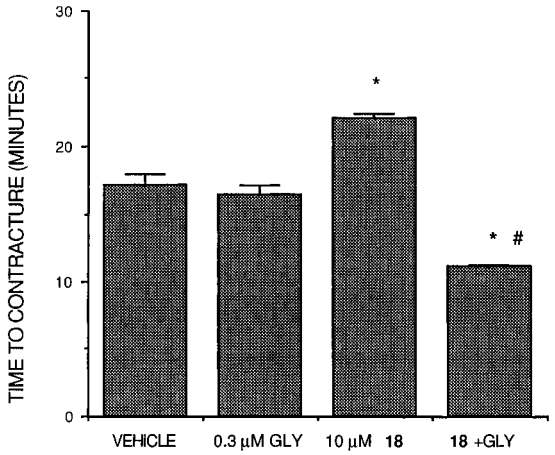



**Figure 2.** The effect of glyburide (gly, 0.3 $\mu$M) on the increase in time to contracture induced by 10 $\mu$M of the pyridylurea **18** ($n$ = 4). While having no effect of its own on the increase in time to contracture (data not shown), glyburide completey abolished the increase in time to contracture seen with compound **18**. The combination of **18** (10 $\mu$M) and glyburide (0.3 $\mu$M) is proischemic as shown by the decrease in time to contracture compared to vehicle treated hearts. * = significantly different from vehicle treated hearts; # = significantly different from hearts treated with compound **18**.

## Conclusion

We have shown that the simplified acyclic analog **18** retains the antiischemic potency and selectivity of its predecessor benzopyran-based compounds (e.g., **4**). The substituent at the ortho-position of **18**, which presumably mimics the gem dimethyl group at the C2 position of the benzopyran ring of **4**, is the most sensitive group to structural changes. The phenoxy group of **18** appears to be optimum as the corresponding *tert*-butyl (**8**) and biphenyl (**16**) analogs are less potent than **18** as antiischemic agents. The results described herein also demonstrate that the benzopyran ring of **4** is not mandatory for antiischemic activity and cardiac selectivity. The phenoxy analog **18** is both more potent and cardioselective compared to the reference agent cromakalim. Being structurally simpler compared to the benzopyran-based $K_{ATP}$ openers, compound **18** offers the opportunity to further explore structure−activity relationships for the discovery of novel antiischemic $K_{ATP}$ openers with an improved pharmacological profile (e.g.,

increased potency and cardiac selectivity). The mechanism of action of compounds **18** and its analogs still appears to involve $K_{ATP}$ opening as the increase in time to contracture caused by **18** is abolished by pretreatment with the $K_{ATP}$ blocker glyburide.

## 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 pallets. $^1$H NMR and $^{13}$C NMR spectra were measured on JEOL 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 $^1$H-, $^{13}$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 $^1$H NMR spectra and microanalysis. Karl Fisher analysis was performed in selected cases to confirm the amount of water present.

**7-Cyano-3,4-dihydro-4,4-dimethyl-*N*-phenyl-1(2*H*)-quinolinecarboxamide (6). A. 6-Amino-2,3-dihydro-3,3-dimethyl-1*H*-inden-1-one (20).** A solution of **19**[8] (6.5 g, 31.7 mmol) in methanol (150 mL) was hydrogenated at 15 psi using 5% palladium over charcoal catalyst. The catalyst was filtered off, and the solvent was removed under vacuum to give an off-white solid (5.72 g, 100%) which was used in the next reaction without purification: $^1$H NMR ($CDCl_3$) $\delta$ 7.26 (d, $J$ = 8.2 Hz, 1 H), 6.95 (m, 2 H), 3.82 (br s, 2 H), 2.55 (s, 2 H), 1.34 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 206.3, 154.5, 146.1, 136.3, 124.0, 123.0, 107.1, 53.4, 37.7, 30.0.

**B. 6-Bromo-2,3-dihydro-3,3-dimethyl-1*H*-inden-1-one (21).** To a solution of compound **20** (6.02 g, 34.4 mmol) in 48% aqueous hydrobromic acid (9.7 mL) and ethanol (30 mL) at 0 °C was added sodium nitrite until a positive starch iodide test was obtained. The resulting diazonium salt solution at 0 °C was added via a pipette to a mixture of CuBr (5.42 g, 18.9 mmol) and 48% aqueous hydrobromic acid at 95 °C. The reaction mixture was heated at reflux temperature for 15 min, cooled to room temperature, and partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium bicarbonate and brine, dried over $MgSO_4$, and evaporated *in vacuo* to obtain an orange solid (7.33 g). The crude product was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (4:1) to obtain the title compound (6.52 g, 79%) as a yellow solid: mp 117−118 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.74 (d, $J$ = 1.76 Hz, 1 H), 7.64 (dd, $J$ = 2.34 and 8.21 Hz, 1 H), 7.32 (d, $J$ = 8.21 Hz, 1 H), 2.53 (s, 2H), 1.34 (s, 6H); $^{13}$C NMR ($CDCl_3$) $\delta$ 204.7, 162.8, 138.2, 137.7, 126.79, 125.8, 122.1, 53.4, 38.9, 30.3; mass spectrum (CI), $m/z$ 239.

**C. 6-Bromo-2,3-dihydro-3,3-dimethyl-1*H*-inden-1-one Oxime (22).** A solution of compound **21** (6.52 g, 27.3 mmol) in ethanol (130 mL) containing hydroxylamine hydrochloride (3.79 g, 54.5 mmol) and sodium acetate (4.03 g, 49.1 mmol) was heated at reflux temperature for 2.5 h. The solvent was removed under vacuum, and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to obtain the title compound (6.94 g, 100%) as a yellow solid, mp 115−117 °C. The crude product was used in the next step without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 7.85 (s, 1H), 7.48 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 7.16 (d, $J$ = 8.21 Hz, 1 H), 2.89 (s, 2 H), 1.34 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 161.0, 155.9, 136.2, 133.6, 124.5, 121.1, 42.7, 41.0, 30.1.

**D. 6-Bromo-2,3-dihydro-3,3-dimethyl-1*H*-inden-1-one Oxime, 4-Methylbenzenesulfonate (23).** To a solution of **22** (5.30 g, 20.9 mmol) in pyridine (50 mL) at 0 °C was added *p*-toluenesulfonyl chloride (4.77 g, 25.0 mmol). The reaction mixture was warmed to room temperature and stirred for 18 h. It was diluted with ethyl acetate, washed with cold dilute hydrochloric acid, water, saturated $NaHCO_3$ solution and brine, and dried over $MgSO_4$. The solvent was removed under vacuum to obtain an orange residue (8.74 g, 100%) which slowly solidified on standing. The compound was used in the next step without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 7.93 (d, $J$ = 8.21 Hz, 2 H), 7.74 (d, $J$ = 2.35 Hz, 1 H), 7.54 (dd, $J$ = 2.35 and 8.80 Hz, 1 H), 7.37 (d, $J$ = 8.21 Hz, 2 H), 7.16 (d, $J$ = 8.21 Hz, 1 H), 2.87 (s, 2 H), 2.45 (s, 3 H), 1.29 (s, 6 H).

**E. 7-Bromo-1,2,3,4-tetrahydro-4,4-dimethylquinoline (24).** To a solution of **23** (7.74 g, 19.0 mmol) in methylene chloride (95.0 mL) at −78 °C was added diisobutylaluminum hydride (1 M solution in hexane, 95.0 mL). The reaction mixture was stirred for 30 min at −78 °C followed by 5 h at 0 °C. The reaction mixture was diluted with methylene chloride (200 mL) and quenched (while stirring vigorously) by the addition of sodium fluoride (16.0 g) and water (5 mL). The reaction mixture was filtered, and the filtrate was dried over $MgSO_4$. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 15% ethyl acetate in hexane to obtain the title compound (2.23 g, 49%) as a light yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 6.93 (d, $J$ = 8.21 Hz, 1 H), 6.63 (dd, $J$ = 2.34 and 8.20 Hz, 1 H), 6.50 (d, $J$ = 1.76 Hz, 1 H), 3.85 (broad s, 1 H), 3.21 (dt, $J$ = 2.93 and 5.86 Hz, 2 H), 1.62 (t, $J$ = 5.86 Hz, 2 H), 1.18 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 144.9, 128.9, 127.8, 119.8, 119.5, 116.2, 38.3, 36.7, 31.5, 30.6, 30.4.

**F. 1,2,3,4-Tetrahydro-4,4-dimethylquinoline-7-carbonitrile (25).** A mixture of **24** (2.24 g, 9.33 mmol) and CuCN (1.67 g, 18.7 mmol) in *N*-methylpyrrolidinone (22.5 mL) was heated at 185−190 °C for 3 h. The reaction mixture was diluted with ethyl acetate and filtered. The filtrate was evaporated, and the residue was purified by flash chromatography on silica gel, eluting with 15% ethyl acetate in hexane to obtain the desired product (0.92 g, 53%) as a light yellow oil: $^1$H NMR ($CDCl_3$) $\delta$ 7.21 (d, $J$ = 7.62 Hz, 1 H), 6.86 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 6.67 (d, $J$ = 1.75 Hz, 1H), 4.12 (broad s, 1 H), 3.34 (t, $J$ = 5.86 Hz, 2 H), 1.72 (t, $J$ = 5.86 Hz, 2 H), 1.28 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 143.9, 134.9, 126.8, 119.9, 119.6, 116.5, 109.9, 38.0, 36.0, 32.05, 30.2; mass spectrum (CI), $m/z$ 187.

**G. 7-Cyano-3,4-dihydro-4,4-dimethyl-*N*-phenyl-1(2*H*)-quinolinecarboxamide (6).** A solution of **25** (0.20 g, 1.07 mmol), phenyl isocyanate (0.13 g, 1.07 mmol), and 4-(dimethylamino)pyridine (50 mg) in acetonitrile (4.5 mL) was heated at reflux temperature for 1 h. The solvent was recovered under vacuum, and the residue was triturated with isopropyl ether to afford the title compound (0.27 g, 83%) as an off-white solid: $^1$H NMR (DMSO-$d_6$) $\delta$ 9.11 (s, 1 H), 7.80 (s, 1 H), 7.54 (m, 3 H), 7.40 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 7.29 (m, 2 H), 7.02 (m, 1 H), 3.79 (t, $J$ = 5.86 Hz, 2 H), 1.78 (t, $J$ = 5.86 Hz, 2 H), 1.30 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 154.5, 142.7, 139.6, 138.4, 128.4, 127.3, 126.6, 125.3, 122.6, 120.0, 118.8, 108.4, 42.0, 37.1, 32.9, 29.1.

**6-Cyano-2,3-dihydro-3,3-dimethyl-*N*-(3-pyridyl)-1*H*-indole-1-carboxamide (7). A. 1-Acetyl-6-bromo-3-methyl-1*H*-indol-2(3*H*)-one (29).** A solution of compound **28**[10a] (9.31 g, 41.2 mmol) in xylene (100 mL) containing acetic anhydride (10 mL) was heated at reflux for 7 h. The reaction mixture was cooled to room temperature and diluted with ethyl acetate. The crude product solution was washed with distilled water followed by saturated sodium bicarbonate solution and brine. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (3:1) to obtain an off-white solid (9.18 g, 78%): mp 102−104 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.34 (s, 1 H), 7.26 (d, $J$ = 8.21 Hz, 1 H), 7.04 (d, $J$ = 8.21 Hz, 1 H), 3.49 (q, 1 H), 2.58 (s, 3H), 1.45 (d, $J$ = 7.62 Hz, 3 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 178.9, 171.2, 141.4, 128.8, 128.5, 124.9, 122.1, 120.2, 41.1, 27.0, 16.2; mass spectrum (CI), $m/z$ 268.

**B. 1-Acetyl-6-bromo-3,3-dimethyl-1*H*-indol-2(3*H*)-one (30).** To a solution of **29** (8.98 g, 33.5 mmol) in dry tetrahydrofuran (115 mL) at 0 °C under argon was added sodium hydride (1.41 g, 35.2 mmol, 60% dispersion in mineral oil).[10b] After stirring for 10 min, methyl iodide (4.75 g, 35.2 mmol) was added dropwise. The reaction mixture was stirred for 2 h at room temperature, quenched by the addition of saturated ammonium chloride solution, and extracted with ethyl acetate. The organic phase was washed with water and brine and dried over magnesium sulfate. The solvent was removed under vacuum to obtain the desired product (9.67g, 100%) as an off-

white solid which was used in the next step without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 8.45 (d, $J$ = 1.76 Hz, 1 H), 7.35 (dd, $J$ = 2.05 and 7.90 Hz, 1 H), 7.11 (d, $J$ = 8.20 Hz, 1 H), 2.68 (s, 3 H), 1.43 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 181.3, 170.8, 139.5, 133.5, 128.2, 123.3, 121.4, 119.8, 44.4, 26.5, 25.1; mass spectrum (CI), *m*/*z* 282.

**C. 6-Bromo-3,3-dimethyl-1*H*-indol-2(3*H*)-one (31).** A solution of compound **30** (9.61 g, 34.1 mmol) in ethanol (80 mL) and 1 N sodium hydroxide (20 mL) was stirred at room temperature for 1 h. The reaction mixture was partitioned between water and diethyl ether. The organic phase was washed with distilled water and brine and dried over magnesium sulfate. The solvent was recovered under vacuum to obtain the desired compound (8.03 g, 98%) as an off-white solid: mp 183−185 °C; $^1$H NMR ($CDCl_3$) $\delta$ 9.05 (broad s, 1 H), 7.18 (dd, $J$ = 1.76 and 8.20 Hz, 1 H), 7.13 (d, $J$ = 1.76 Hz, 1 H), 7.05 (d, $J$ = 7.62 Hz, 1 H), 1.39 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 183.0, 141.1, 135.0, 125.3, 123.9, 121.0, 113.3, 44.5, 24.1.

**D. 6-Bromo-2,3-dihydro-3,3-dimethyl-1*H*-indole (32).** To a solution of **31** (8.0 g, 33.3 mmol) in toluene (185 mL) at 85 °C was added sodium bis(2-methoxyethoxy)aluminum hydride (14.7 mL, 50 mmol, 3.4 M in toluene) over the course of 15 min. After the addition was finished, heating was continued for an additional 15 min at 85 °C. The reaction mixture was cooled to 0 °C and quenched by the addition of 1 N sodium hydroxide solution. The organic phase was separated and washed with 1 N sodium hydroxide and brine. The crude product solution was dried over magnesium sulfate and evaporated *in vacuo* to obtain a tan solid. This material was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (9:1) to obtain the desired product (5.48 g, 73%) as an off-white solid: mp 100−102 °C; $^1$H NMR ($CDCl_3$) $\delta$ 6.85, (s, 1 H), 6.83 (d, $J$ = 1.76 Hz, 1 H), 6.73 (d, $J$ = 1.76 Hz, 1 H), 3.75 (broad s, 1 H), 3.31 (s, 2 H), 1.28 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 152.0, 137.7, 123.50, 121.5, 120.9, 112.6, 62.0, 41.6, 27.8; mass spectrum (CI), *m*/*z* 226.

**E. 1-Acetyl-6-bromo-2,3-dihydro-3,3-dimethyl-1*H*-indole (33).** A solution of compound **32** (5.45 g, 24.1 mmol) in methylene chloride (55 mL) and triethylamine (2.68 g, 26.5 mmol) was cooled to 0 °C and treated with acetyl chloride (2.1 g, 26.5 mmol) dropwise over 5 min. The reaction mixture was stirred for 45 min at room temperature and partitioned between 1 N hydrochloric acid and ethyl acetate. The organic phase was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated *in vacuo* to obtain a pale yellow solid (6.42 g, 99%): mp 95−96 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.29, (s, 1 H), 7.07 (d, $J$ = 8.21 Hz, 1 H), 6.89 (d, $J$ = 8.21 Hz, 1 H), 3.68 (s, 2 H), 2.11 (s, 3H), 1.25 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 168.9, 142.7, 139.4, 126.7, 123.0, 121.1, 119.9, 63.7, 40.0, 28.3, 24.1; mass spectrum (CI), *m*/*z* 268.

**F. 1-Acetyl-2,3-dihydro-3,3-dimethyl-1*H*-indole-6-carbonitrile (34).** The reaction mixture containing **33** (6.56 g, 24.5 mmol) and copper(I) cyanide (4.38 g, 48.9 mmol) in *N*-methylpyrrolidone (70 mL) was heated at 175 °C under argon for 3 h. It was cooled to room temperature, diluted with diethyl ether, and filtered. The filtrate was washed with water, 1 N aqueous hydrochloric acid, saturated sodium bicarbonate, and brine. The product solution was dried over magnesium sulfate and evaporated *in vacuo* to obtain an off-white solid (4.37 g, 83%) which was used for the next reaction without purification: $^1$H NMR ($CDCl_3$) $\delta$ 8.47 (s, 1 H), 7.34 (d, $J$ = 6.45 Hz, 1 H), 7.22 (d, $J$ = 7.62 Hz, 1 H), 3.85 (s, 2 H), 2.24 (s, 3 H), 1.39 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.2, 145.6, 141.9, 128.1, 122.6, 119.8, 119.0, 111.2, 63.3, 40.6, 28.2, 24.0; mass spectrum (CI), *m*/*z* 215.

**G. 2,3-Dihydro-3,3-dimethyl-1*H*-indole-6-carbonitrile (35).** A solution of **34** (4.33 g, 20.2 mmol) in a mixture of acetonitrile (120 mL) and 5 N hydrochloric acid (40 mL) was heated at reflux temperature for 2 h. The reaction mixture was cooled to room temperature and carefully neutralized with saturated sodium bicarbonate solution. The oily layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated *in vacuo* to obtain a brown oil. The crude material was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (3:2) to obtain the desired compound (3.16 g, 91%) as a light yellow solid: $^1$H NMR ($CDCl_3$) $\delta$ 7.06 (d, $J$ = 7.63 Hz, 1 H), 7.00 (dd, $J$ = 1.76 and 7.62 Hz, 1 H), 6.78 (s, 1 H), 3.42 (s, 2 H), 1.31 (s, 6 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 150.5, 143.7, 123.0, 122.5, 119.8, 111.2, 110.5, 61.3, 41.8, 27.2; mass spectrum (CI), *m*/*z* 173.

**H. 6-Cyano-2,3-dihydro-3,3-dimethyl-*N*-(3-pyridyl)-1*H*-indole-1-carboxamide (7).** The reaction mixture containing **35** (0.30 g, 1.74 mmol) and nicotinoyl azide (0.32 g, 2.18 mmol) in toluene (6 mL) was heated at 85 °C for 1 h. It was cooled to room temperature and partitioned between ethyl acetate and water. The organic phase was washed with saturated sodium bicarbonate solution followed by brine. The product solution was dried over magnesium sulfate and evaporated under vacuum to obtain a yellow solid. The crude material was purified by flash chromatography on silica gel, eluting with ethyl acetate to afford the title compound (0.41 g, 80%) as a white solid: $^1$H NMR (DMSO-$d_6$) $\delta$ 8.84 (s, 1 H), 8.32 (d, $J$ = 4.11 Hz, 1 H), 8.22 (s, 1 H), 8.08 (d, $J$ = 8.21 Hz, 1 H), 7.53 (m, 3 H), 7.43 (dd, $J$ = 4.69 and 8.21 Hz, 1 H), 4.07 (s, 2 H), 1.44 (s, 6 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.9, 146.2, 144.0, 143.2, 142.4, 136.3, 127.6, 126.8, 123.9, 123.6, 119.5, 117.5, 110.2, 61.8, 42.0, 28.2; mass spectrum (CI), *m*/*z* 293.

***N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-phenylurea (8). A. 4-(1,1-Dimethylethyl)-3-nitrobenzonitrile (39).** To a solution of **38**[11] (10.0 g, 51.5 mmol) in ethanol (50 mL) at 0 °C was added a solution of concentrated hydrochloric acid (12.5 mL) in ethanol (87.5 mL) followed by a solution of sodium nitrite (3.91g, 56.6 mmol) in water (25 mL). The reaction mixture was stirred at 0 °C for 10 min and added in portions to a solution of copper(I) cyanide (18.45 g) and potassium cyanide (13.41 g) in water (200 mL) at 100 °C. After the addition was finished, the reaction mixture was stirred for 15 min at 100 °C, cooled to room temperature, and partitioned between water and ethyl acetate. The organic fraction was washed with brine, dried over magnesium sulfate, and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (9:1) to afford the desired compound (3.74 g, 42%) as a yellow solid: mp 67−69 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.72 (m, 2 H), 7.62 (m, 1 H), 1.58 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 151.2, 146.8, 133.8, 130.1, 127.3, 116.5, 111.2, 36.4, 30.3.

**B. 3-Amino-4-(1,1-dimethylethyl)benzonitrile (40).** A mixture of **39** (3.74 g, 18.3 mmol) and stannous chloride dihydrate (20.6 g, 91.6 mmol) in ethanol (25 mL) was heated at reflux temperature for 45 min. The reaction mixture was poured into ice-cold water and neutralized with solid sodium bicarbonate. The pH was adjusted to approximately 12 with 50% NaOH solution, and the reaction mixture was extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated *in vacuo* to obtain the desired compound (3.20 g, 100%) as a brown solid. The crude product was used in the next step without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 7.34 (d, $J$ = 8.20 Hz, 1 H), 7.04 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 6.94 (d, $J$ = 1.76 Hz, 1 H), 4.16 (broad s, 2 H), 1.47 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 145.3, 138.4, 127.2, 121.6, 119.7, 119.2, 110.1, 34.5, 29.0; mass spectrum (CI), *m*/*z* 175.

**C. *N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-phenylurea (8).** A solution of **40** (0.40 g, 2.29 mmol) and phenyl isocyanate (0.27 g, 2.29 mmol) in chloroform (4 mL) was heated at reflux temperature for 16 h. The solvent was removed under vacuum, and the residue was crystallized from 2-propanol to obtain an off-white solid (0.46 g, 86%): $^1$H NMR ($CDCl_3$) $\delta$ 9.33 (s, 1 H), 7.90 (s, 1 H), 7.79 (s, 1 H), 7.64 (s, 2 H), 7.56 (d, $J$ = 7.62 Hz, 2 H), 7.37 (m, 2 H), 7.06 (m, 1 H), 1.47 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 153.1, 149.2, 139.8, 137.0, 132.4, 128.8, 128.4, 127.8, 121.9, 118.5, 118.1, 109.0, 35.1, 29.9.

***N*-[(2-Chloro-5-pyridyl)-*N*′-[5-cyano-2-(1,1-dimethylethyl)phenyl]urea (15). A. *N*-Cyano-*N*′-[5-cyano-2-(1,1-dimethylethyl)phenyl]carbamic Acid, Phenyl Ester (41).** A solution of **40** (1.5 g, 8.61 mmol) in methylene chloride (15 mL) and pyridine (1 mL) at 0 °C was treated with phenyl chloroformate (1.42 g, 9.0 mmol). The reaction mixture was stirred for 1 h at ambient temperature and partitioned between ethyl acetate and 1 N hydrochloric acid. The organic phase was washed with saturated sodium bicarbonate solution

and brine and dried over magnesium sulfate. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel eluting with hexane/ethyl acetate (4:1) to afford the desired compound (2.38 g, 94%) as a colorless thick oil: $^1$H NMR ($CDCl_3$) $\delta$ 8.10 (broad s, 1 H), 7.52−7.38 (m, 5 H), 7.28−7.18 (m, 3 H), 1.49 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 152.0, 150.3, 135.9, 129.4, 128.8, 127.6, 125.9, 121.5, 118.2, 110.9, 35.0, 30.3.

**B. *N*-[(2-Chloro-5-pyridyl)-*N*′-[5-cyano-2-(1,1-dimethylethyl)phenyl]urea (15).** A solution of **41** (0.60 g, 2.04 mmol), 5-amino-2-chloropyridine (0.29 g, 2.24 mmol), and (*N*,*N*-dimethylamino)pyridine (50 mg) in *N*,*N*-dimethylformamide (6 mL) was heated at 100 °C for 45 min. The reaction mixture was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic phase was washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (2:1) to obtain a colorless solid (0.63 g, 73%): $^1$H NMR (DMSO-$d_6$) $\delta$ 9.57 (s, 1 H), 8.55 (d, $J$ = 2.35 Hz, 1 H), 8.09 (dd, $J$ = 2.34 and 8.20 Hz, 1 H), 7.99 (s, 1 H), 7.88 (s, 1 H), 7.66 (m, 2 H), 7.49 (d, $J$ = 8.21 Hz, 1 H), 1.46 (s, 9 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 153.1, 149.9, 142.3, 139.4, 136.7, 136.1, 132.8, 129.0, 128.8, 127.9, 124.1, 118.3, 109.2, 35.2, 30.0.

Compounds **9** and **11**−**14** were prepared in a similar manner.

***N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(3-pyridyl)urea (9):** $^1$H NMR ($CD_3OD$) $\delta$ 8.71 (d, $J$ = 2.35 Hz, 1 H), 8.28 (dd, $J$ = 1.18 and 4.69 Hz, 1 H), 8.13 (m, 1 H), 7.86 (d, $J$ = 1.76 Hz, 1 H), 7.72 (d, $J$ = 8.21 Hz, 1 H), 7.62 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 7.46 (dd, $J$ = 4.69 and 8.21 Hz, 1 H), 1.55 (s, 9 H); $^{13}$C NMR ($CD_3OD$) $\delta$ 155.8, 152.1, 144.0, 141.03, 138.2, 137.8, 134.5, 130.7, 129.3, 128.1, 125.3, 119.2, 111.5, 36.4, 30.8.

***N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(2-pyridyl)urea (11):** $^1$H NMR ($CDCl_3$) $\delta$ 11.94 (broad s, 1 H), 9.69 (broad s, 1 H), 8.17 (m, 2 H), 7.71 (m, 1 H), 7.54 (d, $J$ = 8.21 Hz, 1 H), 7.42 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 6.98 (dd, $J$ = 2.93 and 4.11 Hz, 1 H), 6.94 (s, 1 H), 1.52 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.5, 152.8, 147.9, 145.5, 139.1, 136.6, 130.9, 128.2, 127.5, 118.8, 117.6, 112.4, 110.3, 35.3, 29.8.

***N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(4-pyridyl)urea (12):** $^1$H NMR (DMSO-$d_6$) $\delta$ 9.70 (s, 1 H), 8.44 (broad s, 2 H), 8.04 (s, 1 H), 7.87 (s, 1 H), 7.67 (m, 2 H), 7.53 (m, 2 H), 1.45 (s, 9 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.9, 150.2, 150.1, 146.6, 136.5, 133.2, 129.2, 128.0, 118.4, 112.3, 109.2, 35.2, 30.0.

***N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(5-pyrimidinyl)urea (13):** $^1$H NMR (DMSO-$d_6$) $\delta$ 9.58 (s, 1 H), 9.01 (s, 2 H), 8.89 (s, 1 H), 8.14 (s, 1 H), 7.90 (d, $J$ = 1.76 Hz, 1 H), 7.68 (m, 2 H), 1.47 (s, 9 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 153.2, 151.9, 150.2, 146.2, 136.6, 135.2, 133.2, 129.2, 128.0, 118.37, 109.2, 35.2, 30.0.

***N*-[5-Cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(2-pyrazinyl)urea (14):** $^1$H NMR ($CDCl_3$) $\delta$ 11.11 (broad s, 1 H), 10.14 (s, 1 H), 8.42 (s, 1 H), 8.25 (d, $J$ = 2.35 Hz, 1 H), 8.10 (s, 1 H), 8.03 (s, 1 H), 7.57 (d, $J$ = 8.21 Hz, 1 H), 7.48 (d, $J$ = 8.21 Hz, 1 H), 1.49 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.2, 148.9, 148.6, 138.8, 137.7, 136.2, 135.7, 131.6, 129.2, 127.7, 118.4, 110.5, 35.3, 29.9.

***N*″-Cyano-*N*-[5-cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(3-pyridyl)guanidine (10). A. *N*-Cyano-*N*′-[5-cyano-2-(1,1-dimethylethyl)phenyl]carbamimidic Acid, Phenyl Ester (42).** To a solution of **40** (0.25 g, 1.43 mmol) in dry tetrahydrofuran (5 mL) was added sodium hydride (91 mg, 2.3 mmol, 60% oil dispersion). After stirring at room temperature for 15 min, diphenyl cyanocarbonimidate (0.51 g, 2.15 mmol) was added and the reaction mixture was heated at reflux temperature for 4 h. The reaction was quenched by the addition of saturated ammonium chloride solution; the layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate solution and brine, dried over magnesium sulfate, and evaporated. The crude material was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (7:3) to obtain the desired compound (0.35 g, 77%) as an off-white solid: mp 179−181 °C; $^1$H NMR (DMSO-$d_6$) $\delta$ 8.10 (d, $J$ = 1.76 Hz, 1 H), 7.82 (dd, $J$ = 1.76 and 8.21 Hz, 1 H), 7.68 (d, $J$ = 8.80 Hz, 1 H), 7.45 (m, 2 H), 7.33−7.23 (m, 3 H), 1.42 (s, 9 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 153.0, 151.1, 135.2, 135.1, 132.2, 129.7, 129.0, 126.5, 121.5, 117.9, 109.8, 35.8, 30.4.

**B. *N*″-Cyano-*N*-[5-cyano-2-(1,1-dimethylethyl)phenyl]-*N*′-(3-pyridyl)guanidine (10).** A solution of **42** (0.40 g, 1.26 mmol) and 3-aminopyridine (0.14g, 1.51 mmol) in *N*,*N*-dimethylformamide (8 mL) was heated at 100 °C under argon for 4 h. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried over magnesium sulfate, and evaporated. The crude material was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (7:3), and the product was crystallized from 2-propanol to give an off-white solid (0.23 g, 58%): $^1$H NMR (DMSO-$d_6$) $\delta$ 9.21 (s, 1 H), 8.94 (s, 1 H), 8.50 (d, $J$ = 2.35 Hz, 1 H), 8.35 (d, $J$ = 3.52 Hz, 1 H), 7.84 (s, 1 H), 7.78 (m, 2 H), 7.66 (d, $J$ = 8.21 Hz, 1 H), 7.38 (dd, $J$ = 4.69 and 8.21 Hz, 1 H), 1.39 (s, 9 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 157.7, 153.9, 146.2, 145.7, 136.0, 134.6, 132.2, 132.0, 129.3, 123.8, 118.5, 116.1, 110.9, 36.1, 30.7.

***N*-[4-Cyano-(1,1′-biphenyl)-2-yl]-*N*′-(3-pyridyl)urea (16). A. 2-Nitro-(1,1′-biphenyl)-4-carbonitrile (46).** The reaction mixture containing **45**[12] (4.56 g, 16.4 mmol) and copper(I) cyanide (2.94 g, 9.12 mmol) in *N*-methylpyrrolidone (45 mL) was heated at 175−180 °C for 2.5 h. It was cooled to room temperature and diluted with diethyl ether. The precipitated solids were filtered, and the filtrate was washed with water, 1 N hydrochloric acid, saturated sodium bicarbonate solution, and brine. The extract was dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel, eluting with hexane/ethyl acetate (4:1) to obtain the desired compound as a pale yellow solid (2.08 g, 56%): mp 117−119 °C; $^1$H NMR ($CDCl_3$) $\delta$ 8.13 (d, $J$ = 1.17 Hz, 1 H), 7.89 (dd, $J$ = 1.76 and 7.62 Hz, 1 H), 7.60 (d, $J$ = 8.20 Hz, 1 H), 7.45 (m, 3 H), 7.29 (m, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 149.3, 140.7, 135.5, 135.1, 133.1, 129.4, 129.0, 128.6, 127.6, 116.5, 112.4; mass spectrum (CI), $m/z$ 242.

**B. 2-Amino-(1,1′-biphenyl)-4-carbonitrile (47).** A mixture of **46** (1.82 g, 8.12 mmol) and stannous chloride dihydrate (9.16 g, 40.6 mmol) in ethanol (20 mL) was heated at reflux temperature for 45 min. The reaction mixture was poured onto ice/water and neutralized with solid sodium bicarbonate. The pH was adjusted to 12 by the addition of 5 N sodium hydroxide, and the aqueous mixture was extracted with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. The solvent was removed under vacuum, and the residue was triturated with cold pentane to yield an off-white solid (1.40 g, 89%): mp 53−55 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.44 (m, 5 H), 7.17 (d, $J$ = 8.21 Hz, 1 H), 7.07 (dd, $J$ = 1.76 and 9.38 Hz, 1 H), 6.99 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 144.2, 137.6, 131.7, 131.0, 129.1, 128.6, 128.1, 121.9, 119.2, 118.0, 111.8.

**C. *N*-[4-Cyano-(1,1′-biphenyl)-2-yl]-*N*′-(3-pyridyl)urea (16).** Compound **47** was converted (nicotinoyl azide, toluene, heat, 73%) to the desired product **16** by the same procedure as used for the preparation of **7** from **35**. The product was crystallized from 2-propanol to obtain an off-white solid: $^1$H NMR (DMSO-$d_6$) $\delta$ 9.45 (s, 1 H), 8.60 (s, 1 H), 8.50 (s, 1 H), 8.27 (d, $J$ = 4.69 Hz, 1 H), 8.18 (s, 1 H), 7.99 (d, $J$ = 8.21 Hz, 1 H), 7.67−7.47 (m, 7 H), 7.37 (dd, $J$ = 4.69 and 8.79 Hz, 1 H); $^{13}$C NMR (DMSO-$d_6$) $\delta$ 152.6, 143.2, 140.0, 136.9, 136.7, 136.1, 131.8, 129.2, 129.0, 128.6, 126.5, 125.2, 124.8, 123.7, 118.8, 110.5.

***N*-[5-Cyano-2-[[(4-methylphenyl)sulfonyl]amino]phenyl]-*N*′-(3-pyridyl)urea (17). A. *N*-(4-Cyano-2-nitrophenyl)-4-methylbenzenesulfonamide (49).** To a solution of 4-amino-3-nitrobenzonitrile (**48**) (1.90 g, 11.6 mmol) in dimethyl sulfoxide (50 mL) was added sodium hydride (0.56 g, 14 mmol). The resulting red solution was stirred for 5 min and treated with *p*-toluenesulfonyl chloride (2.45 g, 12.8 mmol) in one portion. The reaction mixture was stirred for 30 min, poured into water (200 mL), and basified to pH 12 by the addition of 10% potassium hydroxide. The precipitate (starting material) was filtered off, and the mother liquor was acidified to pH 2 with 10% hydrochloric acid. The precipitate was collected to give the desired product as a light yellow solid (0.6

g, 16%). This material was employed in the next reaction without further purification: $^1$H NMR ($CDCl_3$) $\delta$ 2.35 (s, 3 H), 2.56 (s, 1 H), 7.25 (d, $J$ = 8 Hz, 2 H), 7.69 (dd, $J_1$ = 2 Hz, $J_2$ = 8 Hz, 1 H), 7.64 (d, $J$ = 8 Hz, 2 H), 7.89 (d, $J$ = 8 Hz, 1 H), 8.40 (d, $J$ = 2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 146.5, 138.9, 138.6, 135.9, 131.5, 131.1, 128.2, 120.8, 117.0, 107.6, 22.4.

**B. *N*-(2-Amino-4-cyanophenyl)-4-methylbenzenesulfonamide (50).** To the reaction mixture containing **49** (330 mg, 1.04 mmol) in ethyl acetate (10 mL) was added stannous chloride dihydrate (940 mg, 4.16 mmol) at room temperature. The mixture was stirred at room temperature for 3 h and quenched with saturated $NaHCO_3$ solution (3 mL). The resulting solution was treated with excess $MgSO_4$ and stirred at room temperature for 2 h. The suspension was filtered through a pad of Celite, and the filtrate was concentrated. The residue was crystallized from hexane/ethyl acetate to give a colorless solid (250 mg, 84%): mp 167−168 °C; $^1$HNMR (DMSO-$d_6$) $\delta$ 2.35 (s, 3 H), 6.80 (dd, 1 H), 6.93 (d, $J$ = 2 Hz, 1 H), 6.99 (d, $J$ = 8.2 Hz, 1 H), 7.35 (d, $J$ = 8 Hz, 2 H), 7.62 (d, $J$ = 8.2 Hz, 2 H).

**C. *N*-[5-Cyano-2-[[(4-methylphenyl)sulfonyl]amino]-phenyl]-*N′*-(3-pyridyl)urea (17).** The desired product (**17**) was prepared in 75% yield from **50** and nicotinoyl azide by the same procedure as described for the synthesis of **7** from **35**. The product was crystallized from DMF/ethyl acetate/hexanes to give a colorless powder (170 mg, 75%): $^1$H NMR (DMSO-$d_6$) $\delta$ 9.78 (s, 1 H), 8.61 (d, 2 H), 8.37 (d, $J$ = 2 Hz, 1 H), 8.25 (d, 1 H), 7.61 (d, $J$ = 8 Hz, 2 H), 7.35 (m, 4 H), 6.75 (d, $J$ = 8 Hz, 1 H), 2.34 (s, 3 H).

***N*-(5-Cyano-2-phenoxyphenyl)-*N′*-(3-pyridyl)urea (18). A. 3-Nitro-4-phenoxybenzonitrile (52).** To a solution of 4-chloro-3-nitrobenzonitrile (3.6 g, 20 mmol) and phenol (2.8 g, 30 mmol) in dimethylformamide (75 mL) was added solid potassium carbonate (5 g, 36 mmol), and the suspension was stirred at room temperature for 8 h and at 50 °C for 18 h. The reaction mixture was concentrated, and the residue was diluted with water (500 mL) and extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium bicarbonate and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash column chromatography to give an oil (3.0 g, 63%), which solidified upon standing. The crude product was used in the next reaction: $^1$H NMR ($CDCl_3$) $\delta$ 7.10 (d, $J$ = 8.8 Hz, 1 H), 7.24 (m, 2 H), 7.40 (m, 1 H), 7.55 (m, 2 H), 7.82 (dd, $J$ = 2.4, 8.8 Hz, 1 H), 8.34 (d, $J$ = 2.4 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 155.0 153.0 140.0, 137.2, 130.5, 129.9, 126.3, 120.4, 119.1, 116.5, 115.0, 106.1.

**B. 3-Amino-4-phenoxybenzonitrile (53).** The title compound was prepared (88%) from **52** by the same procedure as described for the preparation of **50** from **49**. The product was obtained as a colorless solid: mp 74−75 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.14 (broad s, 2 H), 6.79 (d, $J$ = 8 Hz, 1 H), 6.99 (dd, $J$ = 2, 8 Hz, 1 H), 7.08 (m, 3 H), 7.24 (m, 1 H), 7.42 (m, 2 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 155.0, 148.0, 138.0, 130.0, 124.4, 122.8, 119.1, 118.4, 117.6, 106.0.

**C. *N*-(5-Cyano-2-phenoxyphenyl)-*N′*-(3-pyridyl)urea (18).** The preparation of **18** from **53** was carried out in 70% yield by the same procedure as described for the synthesis of **7** from **35**. The product was crystallized from ethyl acetate/methanol/hexane to give a colorless solid: $^1$H NMR ($CDCl_3$) $\delta$ 6.55 (d, $J$ = 8 Hz, 1 H), 6.88−7.28 (m, 7 H), 7.91 (m, 1 H), 8.02 (d, $J$ = 3.5 Hz, 1 H), 8.33 (d, $J$ = 2.4 Hz, 1 H), 8.54 (m, 2 H), 9.20 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 154.0, 152.0, 149.0, 142.1, 138.9, 136.0, 130.0, 129.8, 125.7, 125.5, 124.8, 123.3, 122.1, 119.6, 115.7, 106.0.

**Biological Assays.** $EC_{25}$ values for increasing time to contracture were determined in isolated perfused globally ischemic rat hearts. To compare the antiischemic vs peripheral vasodilator potencies, we determined $IC_{50}$ values for relaxation of the methoxamine contracted rat aorta. Experimental details of both methods are described.[6]

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