where ΔA is the difference in absorption at 340 nm before and after the reaction.

Registry No. 1, 86404-04-8; 1a, 86404-03-7; 2, 132530-91-7; 3, 88306-62-1; 4, 106396-33-2; 5, 88306-73-4; 6, 133794-55-5; 7, 133794-56-6; 8, 133794-57-7; 9, 133794-58-8; 10, 133794-59-9; 11, 132530-92-8; 12, 26633-25-0; 13, 139870-17-0; 14, 139870-18-1; 15, 69677-84-5; 16, 139870-19-2; 17, 139870-20-5; 17 (2-*O*-benzyl derivative), 139870-23-8; 18, 137-66-6; 19, 98829-12-0; 20, 15042-01-0; 21 (R = CH_2COCH_3), 139870-21-6; 22 (R = CH_2COCH_3), 139870-22-7; $ClCH_2COCH_3$, 78-95-5; $CH_3(CH_2)_{14}COCl$, 112-67-4; 3-*O*-acetonyl-5,6-*O*-isopropylideneascorbic acid, 126100-80-9.

Synthesis and Antihypertensive Activity of 3-[(Substituted-carbonyl)amino]-2*H*-1-benzopyrans

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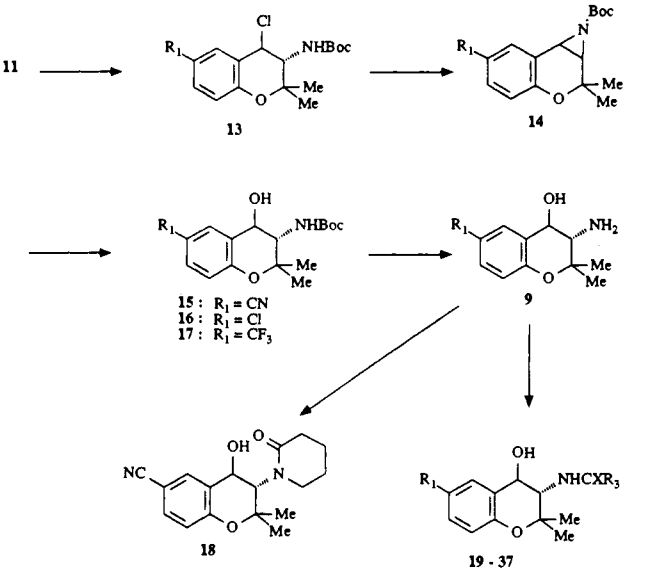
The synthesis and antihypertensive activity of a series of novel 3-[(subtituted-carbonyl)amino]-2*H*-1-benzopyran-4-ols, administered orally to spontaneously hypertensive rats, are described. Optimum activity in this series was observed for compounds with branched alkyl or branched alkylamino groups flanking the carbonyl or thiocarbonyl group (21, 31-33), which were approximately equipotent to cromakalim. Replacement of the 4-hydroxyl group by hydrogen, methoxy, or amino in this series only led to a slight reduction in potency. These observations are in marked contrast to the structure-activity relationships previously found for the 4-amidobenzopyran-3-ols. The antihypertensive activity of representative compounds 15 and 33 was attenuated by preatreatment with glibenclamide, and thus these compounds may belong to the series of drugs which have been classified as potassium channel activators.

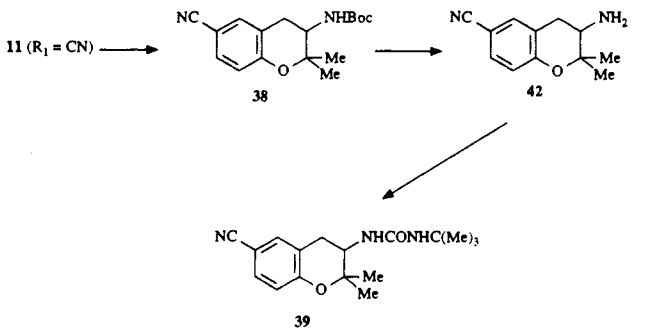
Recently we have described several series of novel antihypertensive agents based on the 4-(2-oxopyrrolidin-1-yl)-2*H*-1-benzopyran-3-ol cromakalim (1),[1-4] which has been shown to hyperpolarize the membrane potential of vascular smooth muscle cells[5] via enhanced efflux of potassium ions[6] through ATP-sensitive channels.[7] The net effect of this process is to relax blood vessels and reduce blood pressure.[8]

Since the discovery[9] of cromakalim (1) a number of other compounds such as pinacidil (2) and RP 49356 (3) have been reported[10] to be potassium channel activators. Sev-

Scheme I



Scheme II



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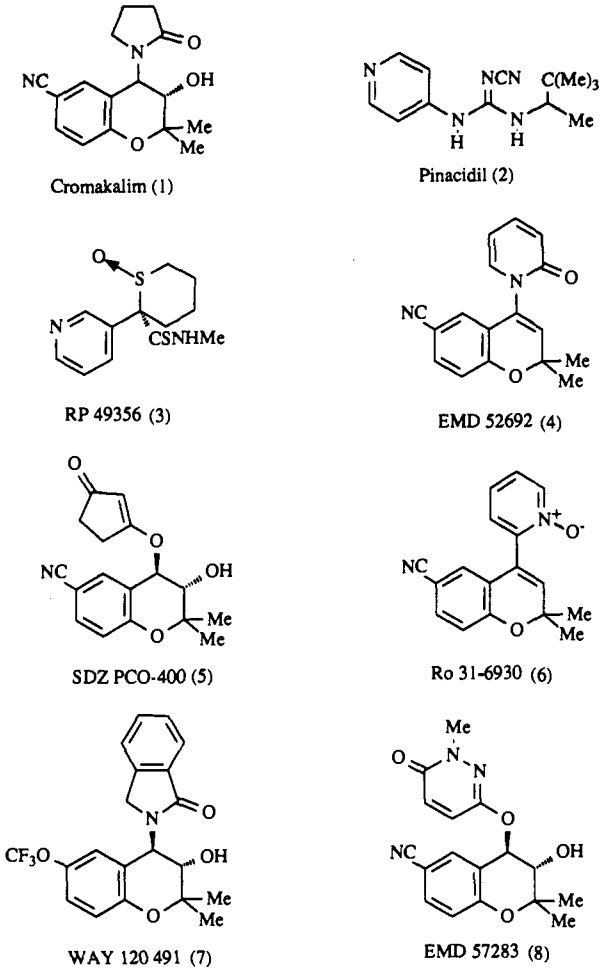


Figure 1.

eral benzopyran-based potassium channel activators such as EMD 52692 (4),[11] SDZ PCO-400 (5),[12] Ro 31-6930 (6),[13] WAY 120 491 (7),[14] and EMD 57283 (8)[15] have also appeared recently (see Figure 1).

As can be seen from the benzopyran potassium channel activators reported thus far, work has concentrated on finding effective replacements for the 4-(2-oxopyrrolidin-1-yl) group or the 6-cyano substituent found in cromalkalim (1). As part of our ongoing chemical program based around cromakalim (1) we have investigated the effect on antihypertensive activity of transposing the 4-amido and 3-hydroxyl substituents on the benzopyran ring. This paper describes the synthesis of a series of 3-[(substituted-carbonyl)amino]-2*H*-1-benzopyrans and their evaluation in spontaneously hypertensive rats (SHR).

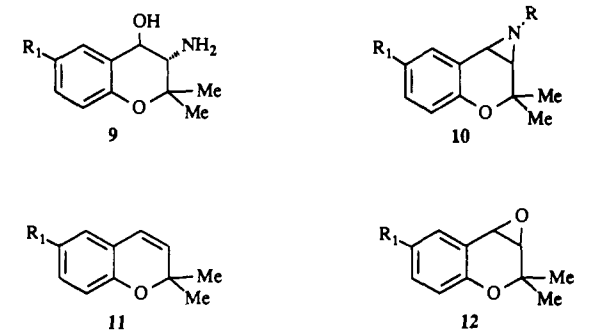
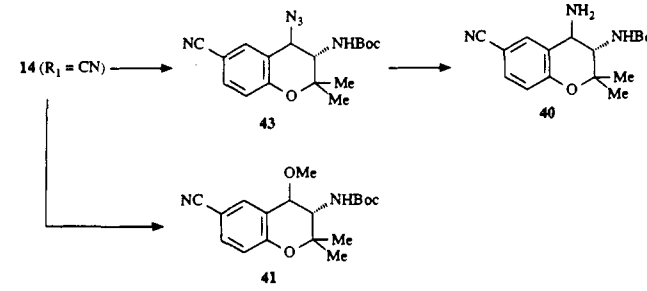


Figure 2.

Scheme III



Chemistry

We considered that convenient starting materials for 3-amino-4-hydroxy-2*H*-1-benzopyrans **9** would be the protected aziridines **10** (see Figure 2). Attempted preparation of **10** (R_1 = CN) from either chromene **11** (R_1 = CN) or epoxide **12** (R_1 = CN) using literature methods[16-18] was unsuccesful. However, treatment of chromene **11** (R_1 = CN) with *tert*-butyl *N,N*-dichlorocarbamate in toluene at 50 °C, followed by in situ reduction with sodium metabisulphite led, in a regio- and stereoselective manner, to *trans*-chloro carbamate **13** (R_1 = CN) (Scheme I), which on treatment with K_2CO_3 in aqueous EtOH gave Boc-protected aziridine **14** (R_1 = CN) in good overall yield.[19] Reaction of **14** (R_1 = CN) with 1% H_2SO_4 in aqueous dioxane gave **15**, which was deprotected with TFA to give the required 3-amino-4-hydroxybenzopyran **9** (R_1 = CN). A similar sequence for chromenes **11** (R_1 = Cl, CF_3) gave **16** and **17**, respectively, which were then deprotected to amino alcohols **9** (R_1 = Cl, CF_3). Treatment of amino alcohol **9** (R_1 = CN) with chlorobutyryl chloride, followed by reaction of the intermediate chloroamide with NaH in THF gave piperidinone **18**. Reaction of **9** with the appropriate acid chloride (method A) or isocyanate (method B) gave compounds **19–37** (see Table I). The regioselectivity of the addition of *tert*-butyl *N,N*-dichlorocarbamate to chromenes was utilized again for the synthesis of chromans **38** and **39** (Scheme II). Thus, reaction of **11** (R_1 = CN) with *tert*-butyl *N,N*-dichlorocarbamate in toluene at 50 °C, followed by replacement of solvent with aqueous dioxane and reduction with zinc dust at 0 °C gave protected amine **38**, and deprotection with TFA to **42**, followed by treatment with *tert*-butyl isocyanate gave **39**. Ring-opening of aziridine **14** (R_1 = CN) with

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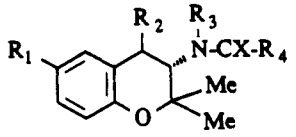
Table I. 3-[(Substituted-carbonyl)amino]-2*H*-1-benzopyrans



compd	R_1	R_2	R_3	R_4	X	method[a]	% yield	mp, °C[b]	recryst[c] solvent	formula	anal.[d]	dose, mg/kg po	max fall[e] in BP, % ± SEM
15	CN	OH	H	$OC(Me)_3$	O	*a*	52	150–152	E	$C_{17}H_{22}N_2O_4$	C,H,N	10.0	−49 ± 5
												3.0	−30 ± 12
												1.0	−14 ± 4
18	CN	OH		$-(CH_2)_4-$	O	*a*	17	222–225	EP	$C_{17}H_{20}N_2O_3$	C,H,N	10.0	−16 ± 1
												3.0	−20 ± 2
19	CN	OH	H	Me	O	A	56	179–181	EP	$C_{14}H_{16}N_2O_3$	C,H,N	10.0	−32 ± 5
												3.0	−14 ± 4
20	CN	OH	H	$CH(Me)_2$	O	A	40	176–178	EP	$C_{16}H_{20}N_2O_3$	C,H,N	0.3	−39 ± 1
												0.1	−22 ± 3
21	CN	OH	H	$C(Me)_3$	O	A	48	186–188	EP	$C_{17}H_{22}N_2O_3$	C,H,N	1.0	−36 ± 5
												0.3	−30 (2)
22	CN	OH	H	$CH_2C(Me)_3$	O	A	44	174–176	EP	$C_{19}H_{24}N_2O_3$	C,H,N	3.0	−27 ± 4
												1.0	−9 ± 3
23	CN	OH	H	C_6H_{11}	O	A	31	208–210	EP	$C_{19}H_{28}N_2O_3$	C,H,N	3.0	−9 ± 3
												1.0	−11 ± 4
24	CN	OH	H	C_6H_5	O	A	40	183–185	EP	$C_{19}H_{18}N_2O_3$	C,H,N	3.0	−20 ± 3
25	CN	OH	H	4-F-C_6H_4	O	A	60	212–215	EP	$C_{19}H_{17}N_2O_3F\cdot H_2O$	C,H,N	3.0	−42 ± 4
												1.0	−22 ± 5
26	CN	OH	H	3,4-F_2-C_6H_3	O	A	35	220–222	EP	$C_{19}H_{16}N_2O_3F_2$	C,H,N	3.0	−37 (1)
												1.0	−6 ± 7
27	CN	OH	H	2-C_5H_4N	O	A	20	216–219	EPM	$C_{18}H_{17}N_3O_3$	C,H,N	3.0	−15 ± 5
												1.0	−18 ± 0
28	CN	OH	H	NHMe	O	B	58	217 dec	C	$C_{14}H_{17}N_3O_3\cdot 0.5H_2O$	C,H,N	10.0	−24 ± 1
												3.0	−8 ± 1
29	CN	OH	H	$NHCH_2Me$	O	B	19	173–175	EP	$C_{15}H_{19}N_3O_3$	C,H,N	3.0	−18 ± 3
												1.0	−13 ± 3
30	CN	OH	H	$NH(CH_2)_2Me$	O	B	32	190–193	EPM	$C_{16}H_{21}N_3O_3$	C,H,N	3.0	−32 ± 3
												1.0	−10 ± 3
31	CN	OH	H	$NHCH(Me)_2$	O	B	46	198–200	EPM	$C_{16}H_{21}N_3O_3$	C,H,N	1.0	−26 ± 2
												0.3	−22 ± 4
32	CN	OH	H	$NHCH(Me)_2$	S	B	49	100 dec	MC	$C_{16}H_{21}N_3O_2S$	C,H,N	0.3	−49 ± 3
33	CN	OH	H	$NHC(Me)_3$	O	B	39	129–132	C	$C_{17}H_{23}N_3O_3\cdot 0.5H_2O$	C,H,N	1.0	−63 (1)
												0.3	−40 ± 2
												0.1	−19 ± 2
34	CN	OH	H	NH-C_6H_{11}	O	B	21	182–183	C	$C_{19}H_{25}N_3O_3$	C,H,N	3.0	−14 ± 3
35	CN	OH	H	$N(Me)_2$	O	B	30	210–212	EM	$C_{15}H_{16}N_3O_3$	C,H,N	3.0	−27 ± 5
36	Cl	OH	H	$NHC(Me)_3$	O	B	40	190–193	EP	$C_{16}H_{23}N_2O_3Cl$	H,N:C[f]	3.0	−34 ± 3
												0.3	−16 ± 3
37	CF_3	OH	H	$NHC(Me)_3$	O	B	73	193–195 dec	EP	$C_{17}H_{23}N_2O_3F_3$	C,H,N	1.0	−31 ± 2
38	CN	H	H	$OC(Me)_3$	O	*a*	71	141–142	EP	$C_{17}H_{22}N_2O_3$	C,H,N	10.0	−30 ± 4
												3.0	−26 ± 6
39	CN	H	H	$NHC(Me)_3$	O	*a*	55	208–211	EP	$C_{17}H_{23}N_3O_2$	C,H,N	0.3	−27 ± 4
40	CN	NH_2	H	$OC(Me)_3$	O	*a*	73	123–126	E	$C_{17}H_{23}N_3O_3$	M^+	10.0	−25 ± 3
41	CN	OCH_3	H	$OC(Me)_3$	O	*a*	29	121–123	EP	$C_{18}H_{24}N_2O_4$	C,H,N	3.0	−39 ± 3
cromakalim												1.0	−47 ± 1
												0.3	−39 ± 11
												0.1	−13 ± 5

[a] See Experimental Section. [b] dec = decomposition. [c] E = EtOAc, C = CH_2Cl_2, M = methanol, P = pentane. [d] Analyses for the elements indicated were within ±0.4% of the theoretical values. [e] Systolic blood pressure was measured at intervals from 1 to 6 h in groups of five SHR per compound. On occasions, pulses were determined from only (*n*) SHR. [f] Calcd: C, 58.80; found: C, 59.24.

NaN_3 (Scheme III) gave exclusively *trans*-azido carbamate **43**, which was reduced with 1,3-propanedithiol in methanol[20] to **40**. Treatment of **14** (R_1 = CN) with $BF_3\cdot Et_2O$ in methanol gave **41**.

Results and Discussion

Compounds were evaluated for oral antihypertensive activity in SHR. Systolic blood pressure, recorded from the tail, was determined before dosing and at various time intervals during the ensuing 6 h. Maximum falls in blood pressure obtained for all the compounds (Table I) occurred at 1–4 h postdose with some recovery to the predose level of blood pressure being observed at 6 h.

Surprisingly, the 4-hydroxy-3-*tert*-butyl carbamate **15** showed good activity at 3 mg/kg, and this result provided the encouragement for further investigation of this series (Table I). In marked contrast to the results obtained previously,[1] where a piperidinone substituent at the 4-position of a 3-hydroxybenzopyran was shown to confer high antihypertensive potency, the 4-hydroxy-3-piperidinone **18** showed only weak activity at the highest dose tested. The acetamide **19** was also less potent than **15**, again in contrast to the structure–activity relationship observed in the 4-substituted series.[2] However, replacement of the methyl group of **19** by isopropyl (**20**) or

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tert-butyl (**21**) groups gave compounds with enhanced potency compared to **15**. Isopropylamide **20** was approximately equipotent to cromakalim, and approximately 3-fold more potent than *tert*-butylamide **21**. Isosteric replacement of the carbamate oxygen atom in **15** by CH_2 gave **22**, a compound of very similar potency to **15**. Interestingly, cyclization of the isopropyl group in **20** to cyclohexyl, as in **23**, resulted in a marked decrease in potency. We have shown previously[2] that aromatic amides confer high potency in the 4-amidobenzopyran series. However, attachment of these substituents at the 3-position, as in **24–27**, did not enhance potency compared to carbamate **15**. Replacement of the carbamate oxygen of **15** by NH gave a series of ureas and, as observed for the amides **19–21** above, increasing the size of the alkyl substituent gave compounds with increasing potency. Thus, the methylurea **28** showed only modest activity at the highest dose tested, but sequential replacement of methyl by ethyl **29** and then *n*-propyl **30** gave compounds of similar potency to **15**. The potency of **28** was also enhanced by substitution of an additional methyl group on the urea nitrogen, as in **35**, which was approximately equipotent with **15**. Incorporation of branched alkyl substituents gave the most potent compounds in this series, with isopropyl **31** and *tert*-butylurea **33** being approximately 3- and 10-fold more potent than **15**, respectively. This requirement for a branched alkyl substituent on the urea for high potency in this series of compounds contrasts markedly with the results obtained in the 4-substituted benzopyran-3-ols where potency was dramatically attenuated when a *tert*-butylurea was introduced.[2] The potency of **31** was further enhanced by thiourea **32** formation, a result which again is in contrast to that reported previously for the 4-substituted series,[2] where thiourea formation decreased potency. As observed for cyclohexylamide **23**, replacement of isopropyl or *tert*-butyl by cyclohexyl **34** in the urea series caused a marked decline in potency. Removal of the 4-hydroxy substituent as in **38** and **39** retained activity, with **38** and **39** being similar in potency to **15** and **33**, respectively. These results contrast with those found previously in the 4-substituted series,[1,2] where removal of the 3-hydroxy substituent led to a 3–10-fold reduction in potency. Replacement of the 4-hydroxy substituent by NH_2, as in **40**, or by OMe, as in **41**, also resulted in compounds of similar potency compared to **15**. In agreement with our observations in the cromakalim series,[1] replacement of the 6-cyano substituent of **33** by chloro, as in **36**, caused a reduction in potency. However, whereas in the cromakalim series a 6-CF_3 substituent was shown to maintain activity,[3] **37** was only approximately one-third as potent as **33**.

Our studies on the transposition of the 4-amido and 3-hydroxyl substituents found in cromakalim have, therefore, revealed a series of acyclic amides and ureas of similar antihypertensive activity to cromakalim (Table I), where the steric requirement for substitution on the amide or urea is tightly defined. Furthermore, the antihypertensive activity of **15** and **33** was blocked by pretreatment with glibenclamide, and these compounds, therefore, can be classified as potassium channel activators.[21]

Experimental Section

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. IR, NMR, and mass spectra, which were in agreement with the structures cited, were recorded on a Perkin-Elmer 197 or 599 IR, a Varian EM 360A at 60 MHz, a Bruker AC250 at 250 MHz, or a JEOL GX 270, and a VG70-70 or 70 ZAB at 70 eV mass spectrometer, respectively. HF_{254} silica gel plates were used for chromatotron chromatography (radial chromatography), and Kieselgel 60 for column chromatography. Anhydrous Na_2SO_4 was used as a drying agent for organic extractions throughout. Petroleum ether refers to the fraction boiling at 60–80 °C. All solvent evaporation was performed under vacuum.

***trans*-3-[(*tert*-Butoxycarbonyl)amino]-4-chloro-3,4-dihydro-2,2-dimethyl-6-substituted-2*H*-1-benzopyrans (13).** A solution of *tert*-butyl *N*,*N*-dichlorocarbamate (12 mmol) in dry PhMe (10 mL) was added dropwise to a solution of the appropriate 2,2-dimethyl-6-substituted-2*H*-1-benzopyran **11**[1] (11 mmol) in dry PhMe (15 mL) at 35–40 °C under N_2. The solution was then stirred at 50 °C for 6 h and cooled to 0 °C, and a 20% solution of $Na_2S_2O_5$ in H_2O (40 mL) was added. The mixture was stirred vigorously for 18 h, and the layers were separated. The organic layer was washed with H_2O, $NaHCO_3$ solution, and brine, and then dried, and the solvents were evaporated. Trituration of the residue with pentane–EtOAc (95:5) gave compounds **13** as colorless solids in yields of 55–70%. Compound **13** (R_1 = CN): 58%; mp 164–166 °C (EtOAc–petroleum ether); NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.46 (s, 9 H), 1.53 (s, 3 H), 4.17 (t, J = 8, 8 Hz, 1 H), 4.63 (d, J = 8 Hz, 1 H), 4.88 (d, J = 8 Hz, N*H*), 6.92 (d, J = 9 Hz, 1 H), 7.48 (dd, J = 9, 2 Hz, 1 H), 7.82 (d, J = 2 Hz, 1 H). Anal. ($C_{17}H_{21}N_2O_3Cl$) C, H, N.

1-(*tert*-Butoxycarbonyl)-1,1a,2,7b-tetrahydro-2,2-dimethyl[1]benzopyrano[3,4-*b*]azirines (14). A solution of the appropriate *trans*-4-chloro-3,4-dihydro-2,2-dimethyl-3-(*tert*-butoxycarbonyl)amino]-6-substituted-2*H*-1-benzopyran **13** (5 mmol) and K_2CO_3 (7 mmol) in EtOH (100 mL) and H_2O (5 mL) was stirred for 18 h. Solvents were evaporated, and the residue was extracted with EtOAc. The combined extracts were dried and evaporated to give the title compounds **14** (90–98%) as crude solids which were characterized by NMR and high-resolution MS before conversion to **15–17**, **40**, and **41**. Compound **14** (R_1 = CN): NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.46 (s, 9 H), 1.65 (s, 3 H), 3.05 (d, J = 6 Hz, 1 H), 3.50 (d, J = 6 Hz, 1 H), 6.86 (d, J = 9 Hz, 1 H), 7.49 (dd, J = 9, 2 Hz, 1 H), 7.65 (d, J = 2 Hz, 1 H); mass spectrum, observed M^+ at m/z 300.1473; $C_{17}H_{20}N_2O_3$ requires 300.1474. Compound **14** (R_1 = Cl): NMR ($CDCl_3$) δ 1.20 (s, 3 H), 1.45 (s, 9 H), 1.62 (s, 3 H), 3.00 (d, J = 6 Hz, 1 H), 3.44 (d, J = 6 Hz, 1 H), 6.75 (d, J = 9 Hz, 1 H), 7.15 (dd, J = 9, 2 Hz, 1 H), 7.32 (d, J = 2 Hz, 1 H). Compound **14** (R_1 = CF_3): NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.45 (s, 9 H), 1.60 (s, 3 H), 3.02 (d, J = 6 Hz, 1 H), 3.50 (d, J = 6 Hz, 1 H), 6.85 (d, J = 9 Hz, 1 H), 7.40–7.65 (m, 2 H).

***trans*-3-[(*tert*-Butoxycarbonyl)amino]-3,4-dihydro-2,2-dimethyl-6-substituted-2*H*-1-benzopyran-4-ols (15–17).** A solution of the appropriate aziridine **14** (2 mmol) in dioxane (20 mL) and 1% H_2SO_4 (20 mL) was stirred at room temperature for 18 h. Solvents were evaporated, and the residue was partitioned between EtOAc and H_2O. The organic extracts were dried, filtered, and evaporated to give the title compounds as crude solids which were purified by recrystallization (see Table I). Compound **15**: NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.42 (s, 9 H), 1.46 (s, 3 H), 3.50 (br s, OH), 3.85 (dd, J = 9, 8 Hz, 1 H), 4.52 (d, J = 9 Hz, 1 H), 4.70 (d, J = 8 Hz, N*H*), 6.87 (d, J = 9 Hz, 1 H), 7.46 (dd, J = 9, 2 Hz, 1 H), 7.82 (d, J = 2 Hz, 1 H).

***trans*-3-Amino-3,4-dihydro-2,2-dimethyl-6-substituted-2*H*-1-benzopyran-4-ols (9).** Trifluoroacetic acid (18 mL, 106 mmol) was added dropwise to a stirred solution of the requisite *trans*-3-[(*tert*-butoxycarbonyl)amino]-3,4-dihydro-2,2-dimethyl-4-hydroxy-6-substituted-2*H*-1-benzopyran **15–17** (6 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under N_2. The solution was stirred for 8 h at 0 °C, then solvents were evaporated, and the residue was dissolved in EtOAc, which was washed with saturated $NaHCO_3$ solution, dried, filtered, and evaporated to give the crude amino alcohols **9** in yields of 90–95%, which were used without further purification. Compound **9** (R_1 = CN): NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.50 (s, 3 H), 3.15 (d, J = 9 Hz, 1 H), 4.40 (br s, 3 H), 4.65 (d, J = 9 Hz, 1 H), 6.72 (d, J = 9 Hz, 1 H), 7.36 (dd, J = 9, 2 Hz, 1 H), 7.68 (d, J = 2 Hz, 1 H).

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-3-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-4-ol (18).** To a solution of amino alcohol **9** (R_1 = CN, 1.0 g, 4.6 mmol) and Et_3N (1 mL) in CH_2Cl_2

(21) Buckingham, R. E.; Hamilton, T. C.; Howlett, D. R.; Mootoo, S.; Wilson, C. Inhibition by Glibenclamide of the Vasorelaxant Action of Cromakalim in the Rat. *Br. J. Pharmacol.* 1989, *97*, 57–64.

(30 mL) at 0 °C was added 5-chlorovaleryl chloride (0.71 g, 4.6 mmol). The solution was stirred at room temperature for 24 h, then H_2O was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with dilute HCl, H_2O, and brine, dried, filtered, and evaporated to give a solid which was dissolved in dry THF (100 mL) under N_2, and NaH (0.116 g, 80% dispersion, 3.87 mmol) was added. The solution was stirred at 20 °C for 6 days, then H_2O was added cautiously, and the mixture was extracted with EtOAc. The organic layer was dried, filtered, and evaporated, and the residue was chromatographed on silica gel and eluted with EtOAc. Recrystallization gave compound **18** (0.2 g) as colorless needles (see Table I). NMR [$(CD_3)_2SO$] δ 1.32 (s, 3 H), 1.42 (s, 3 H), 1.80 (m, 4 H), 2.45 (m, 2 H), 3.28 (m, 2 H), 3.50 (br s, OH), 4.78 (d, J = 8 Hz, 1 H), 5.10 (d, J = 8 Hz, 1 H), 6.86 (d, J = 9 Hz, 1 H), 7.46 (dd, J = 9, 2 Hz, 1 H), 7.85 (d, J = 2 Hz, 1 H).

Method A. Preparation of Amides 19–27. Amino alcohols **9** (1 mmol) and triethylamine (2 mmol) were stirred in CH_2Cl_2 (25 mL) and cooled to 0 °C. The appropriate acid chloride (1 mmol) was added dropwise to the solution, and the mixture was stirred for 18 h at room temperature. Water was added, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ solution, dried, filtered, and evaporated to give the crude amides, which were purified by recrystallization (see Table I). Compound **21**: NMR ($CDCl_3$) δ 1.16, (s, 9 H), 1.30 (s, 3 H), 1.42 (s, 3 H), 3.30–3.50 (br s, OH), 4.23 (dd, J = 9, 8 Hz, 1 H), 4.50 (d, J = 8 Hz, 1 H), 5.70 (d, J = 9 Hz, N*H*), 6.89 (d, J = 9 Hz, 1 H), 7.48 (dd, J = 9, 2 Hz, 1 H), 7.84 (d, J = 2 Hz, 1 H).

Method B. Preparation of Ureas 28–37. The requisite isocyanate (1 mmol) was added to a stirred solution of the appropriate amino alcohol **9** (1 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The solution was allowed to warm to warm temperature and stirred for 1–24 h. In some cases a precipitate formed and was collected by filtration and recrystallized. In the remainder, solvent was evaporated, and the residue was recrystallized (see Table I). Compound **33**: NMR [$(CD_3)_2SO$] δ 1.27 (s, 3 H), 1.32 (s, 9 H), 1.42 (s, 3 H), 3.88 (m, 1 H), 4.40 (m, 1 H), 5.82 (br s, N*H*), 5.88 (d, J = 6 Hz, OH), 5.95 (d, J = 9 Hz, N*H*), 7.04 (d, J = 9 Hz, 1 H), 7.70 (dd, J = 9, 2 Hz, 1 H), 7.89 (d, J = 2 Hz, 1 H).

3-[(*tert*-Butoxycarbonyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (38). A solution of **11** (R_1 = CN, 1.0 g, 5.4 mmol) and *tert*-butyl *N,N*-dichlorocarbamate (1.1 g, 5.9 mmol) in PhMe (20 mL) was heated at 50 °C for 5 h. Solvent was evaporated, and the residue was dissolved in dioxane (20 mL) at 0 °C, and a solution of NH_4OAc (2.08 g, 27 mmol) in H_2O (20 mL) was added. Zinc dust (1.76 g, 27 mmol) was added portionwise to the vigorously stirred mixture, which was allowed to warm to room temperature over 18 h. The mixture was decanted, diluted with H_2O, and extracted with EtOAc. The organic layer was washed with brine, dried, filtered, and evaporated. The residue was chromatographed, eluting with EtOAc–pentane (1:9) to give a crude product which was recrystallized (see Table I) to give compound **38** (1.17 g): NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.38 (s, 3 H), 1.45 (s, 9 H), 2.70 (dd, J = 15, 4 Hz, 1 H), 3.13 (dd, J = 15, 4 Hz, 1 H), 3.97 (m, 1 H), 4.58 (d, J = 9 Hz, N*H*), 6.87 (d, J = 9 Hz, 1 H), 7.40 (m, 2 H).

3-[[(*tert*-Butylamino)carbonyl]amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (39). Trifluoroacetic acid (5 mL) was added to a stirred solution of **38** (0.5 g, 1.66 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C, and the solution was stirred at 0 °C for 5 h. Solvents were evaporated, the residue was dissolved in EtOAc, and the solution was washed with saturated $NaHCO_3$ solution, H_2O, and brine, dried, filtered, and evaporated to give crude amine **42** (0.24 g, 72%), which was dissolved in dry CH_2Cl_2 (30 mL). The solution was cooled to 0 °C under N_2, and *t*-BuNCO (0.13 g, 1.3 mmol) was added. The reaction mixture was stirred at 20 °C for 48 h, the solvent was evaporated, and the residue was chromatographed, eluting with EtOAc–pentane (1:1). The solid obtained was recrystallized (see Table I) to give compound **38** (0.17 g): NMR ($CDCl_3$) δ 1.29 (s, 9 H), 1.31 (s, 3 H), 1.39 (s, 3 H), 2.70 (dd, J = 15, 4 Hz, 1 H), 3.12 (dd, J = 15, 4 Hz, 1 H), 4.13 (m, 1 H), 4.20–4.35 (m, exchanges with D_2O, 2N*H*), 6.85 (d, J = 9 Hz, 1 H), 7.40 (m, 2 H).

***trans*-4-Azido-3-[(*tert*-butoxycarbonyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (43).** Sodium azide (0.79 g, 12.1 mmol) was added to a stirred mixture of **14** (R_1 = CN, 3.32 g, 11 mmol) and NH_4Cl (0.64 g, 12 mmol) in dry DMF (30 mL). The mixture was heated at 60–65 °C for 5 h, then cooled, and H_2O was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with H_2O and brine, dried, filtered, and evaporated to give a solid which was recrystallized from EtOAc–petroleum ether to give compound **43** (2.9 g, 76%): mp 167–168 °C. Anal. ($C_{17}H_{21}N_5O_3$) C, H, N.

***trans*-4-Amino-3-[(*tert*-butoxycarbonyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran (40).** 1,3-Propanedithiol (1.38 g, 12.8 mmol) was added to a stirred solution of **43** (2.36 g, 6.9 mmol) and Et_3N (1.9 mL, 13.6 mmol) in MeOH (40 mL), and the mixture was stirred for 18 h at 20 °C. The mixture was filtered, solvents were evaporated, and the residue was dissolved in Et_2O and extracted with 2 N HCl (3 × 100 mL). The extracts were basified with NaOH and extracted with EtOAc. The combined organic layers were dried, filtered, and evaporated to give a solid which was recrystallized (see Table I) to give compound **40** (1.6 g).

***trans*-3-[(*tert*-Butoxycarbonyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-4-methoxy-2*H*-1-benzopyran (41).** Boron trifluoride etherate (0.1 mL, 0.8 mmol) was added to a stirred solution of **14** (R_1 = CN, 0.3 g, 0.99 mmol), and the solution was stirred at room temperature for 18 h. Solvents were evaporated, and the residue was purified by radial chromatography, eluting with EtOAc–pentane (3:1) to give a gum which was triturated with EtOAc–pentane (1:9) to give compound **41** (90 mg). See Table I.

Pharmacological Testing. Hypertensive Rats. All of the test compounds were evaluated for antihypertensive activity in conscious spontaneously hypertensive rats (14–24 weeks old), derived from the Japanese (Okamoto) strain. Animals with systolic blood pressure > 180 mmHg (1 mmHg = 133 Pa) were considered to be hypertensive.

Systolic blood pressure was recorded by the tail-cuff method using a W+W blood pressure recorder, Model No. 8005; each determination was the mean of at least five recordings. Blood pressure measurements were made prior to the oral administration of test compound and at intervals for up to 6 h postdose.

All compounds were administered (via an oral dosing needle placed in the esophagus) as a solution or suspension in 1% w/v methylcellulose solution.

With the use of the above procedure, vehicle alone typically has little or no effect on blood pressure apart from a slight reduction (by 5–10%) at 6 h postdose.

Normotensive Rats. Male Sprague Dawley rats with implanted catheters in the aorta and vena cava were used in the glibenclamide block experiments. The arterial catheter was linked to a Bell and Howell physiological pressure transducer (Type 4-442-0001), to allow recording of blood pressure and heart rate, and the venous catheter was linked to a three-way tap. At time 0, timolol, 2 mg/kg iv, was injected, before starting infusion of 5% w/v dextrose. The intravenous infusion was stopped briefly at 30 min to allow injection of glibenclamide, 20 mg/kg, or its vehicle, 5 mg/kg, and again at 60 min when either compound **15** (1 mg/kg) or **33** (0.3 mg/kg) was given to all rats. Blood pressure and heart rate were then monitored during the subsequent 2 h.

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Registry No. **9**, 130867-14-0; **11** (R_1 = CN), 33143-29-2; **13**, 130867-12-8; **14** (R_1 = CN), 130867-13-9; **14** (R_1 = Cl), 130867-16-2; **14** (R_1 = CF_3), 130867-20-8; **15**, 130866-87-4; **18**, 139631-86-0; **19**, 130866-94-3; **20**, 130867-07-1; **21**, 130867-06-0; **22**, 139631-87-1; **23**, 130866-97-6; **24**, 130866-99-8; **25**, 130866-89-6; **26**, 130866-92-1; **27**, 130866-95-4; **28**, 130866-93-2; **29**, 130867-01-5; **30**, 130867-02-6; **31**, 130867-00-4; **32**, 139631-88-2; **33**, 130866-91-0; **34**, 130866-98-7; **35**, 130867-04-8; **36**, 130867-03-7; **37**, 130867-05-9; **38**, 136758-59-3; **39**, 130867-09-3; **40**, 130867-11-7; **41**, 130867-10-6; **42**, 139631-89-3; **43**, 130867-26-4; *tert*-butyl *N,N*-dichlorocarbamate, 54957-94-7; 5-chlorovaleryl chloride, 1575-61-7; *tert*-butyl isocyanate, 1609-86-5.