

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 = CH₂COCH₃), 139870-21-6; 22 (R = CH₂COCH₃), 139870-22-7; ClCH₂COCH₃, 78-95-5; CH₃(CH₂)₄COCl, 112-67-4; 3-*O*-acetyl-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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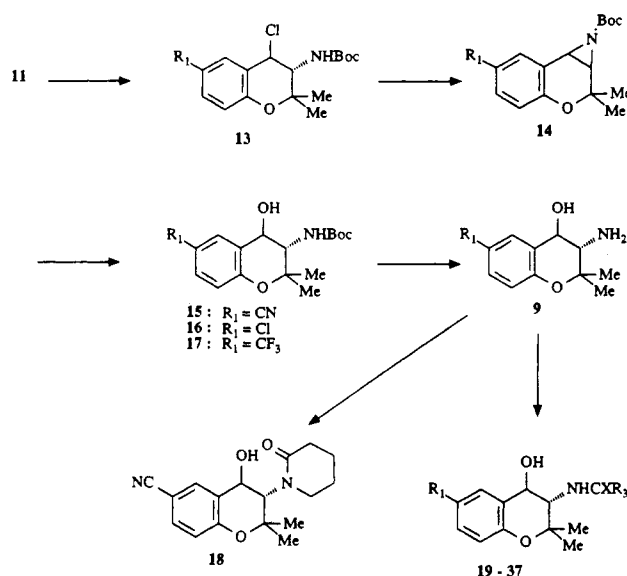
The synthesis and antihypertensive activity of a series of novel 3-[(substituted-carbonyl)amino]-2*H*-1-benzopyran-4-ols, administered orally to spontaneously hypertensive rats, are described. Optimum activity in this series was observed for compounds with branched alkyl or branched alkylamino groups 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 pretreatment 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 cells⁵ via enhanced efflux of potassium ions⁶ through ATP-sensitive channels.⁷ The net effect of this process is to relax blood vessels and reduce blood pressure.⁸

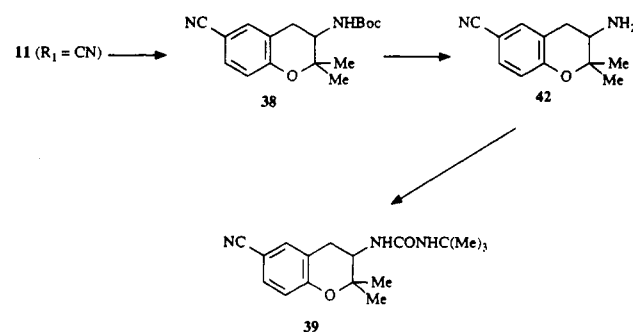
Since the discovery⁹ of cromakalim (1) a number of other

- (1) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. Synthesis and Antihypertensive Activity of 4-(Cyclic amido)-2*H*-1-benzopyrans. *J. Med. Chem.* 1986, 29, 2194-2201.
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Scheme I



Scheme II



compounds such as pinacidil (2) and RP 49356 (3) have been reported¹⁰ to be potassium channel activators. Sev-

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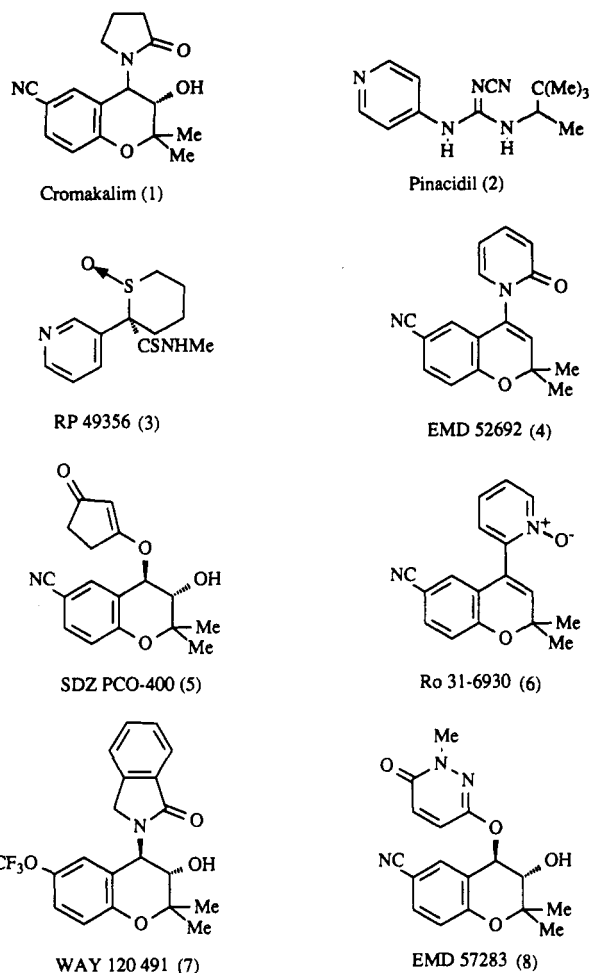


Figure 1.

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 cromakalim (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]-2H-1-benzopyrans and their evaluation in spontaneously hypertensive rats (SHR).

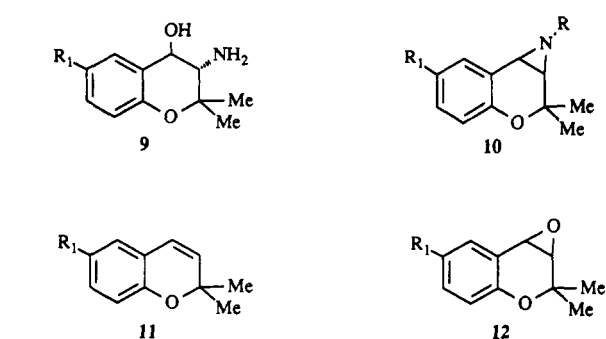
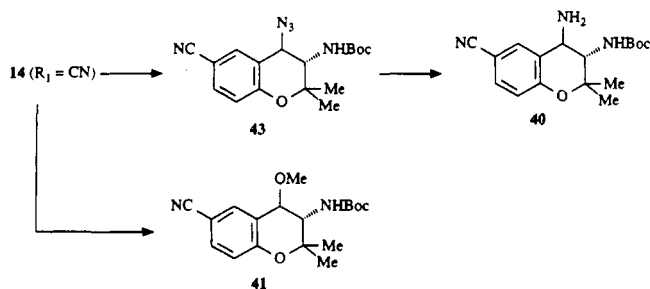


Figure 2.

Scheme III



Chemistry

We considered that convenient starting materials for 3-amino-4-hydroxy-2H-1-benzopyrans 9 would be the protected aziridines 10 (see Figure 2). Attempted preparation of 10 ($R_1 = \text{CN}$) from either chromene 11 ($R_1 = \text{CN}$) or epoxide 12 ($R_1 = \text{CN}$) using literature methods¹⁸⁻¹⁸ was unsuccessful. However, treatment of chromene 11 ($R_1 = \text{CN}$) 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 ($R_1 = \text{CN}$) (Scheme I), which on treatment with K_2CO_3 in aqueous EtOH gave Boc-protected aziridine 14 ($R_1 = \text{CN}$) in good overall yield.¹⁹ Reaction of 14 ($R_1 = \text{CN}$) with 1% H_2SO_4 in aqueous dioxane gave 15, which was deprotected with TFA to give the required 3-amino-4-hydroxybenzopyran 9 ($R_1 = \text{CN}$). A similar sequence for chromenes 11 ($R_1 = \text{Cl}$, CF_3) gave 16 and 17, respectively, which were then deprotected to amino alcohols 9 ($R_1 = \text{Cl}$, CF_3). Treatment of amino alcohol 9 ($R_1 = \text{CN}$) with chlorobutyl 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 ($R_1 = \text{CN}$) 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 ($R_1 = \text{CN}$) with

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Table I. 3-[(Substituted-carbonyl)amino]-2H-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 ₂ O 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 ₂ O ₃	C,H,N	10.0	-16 ± 1
19	CN	OH	H	Me	O	A	56	179–181	EP	C ₁₄ H ₁₆ N ₂ O ₃	C,H,N	10.0	-20 ± 2
20	CN	OH	H	CH(Me) ₂	O	A	40	176–178	EP	C ₁₆ H ₂₀ N ₂ O ₃	C,H,N	0.3	-39 ± 1
21	CN	OH	H	C(Me) ₃	O	A	48	186–188	EP	C ₁₇ H ₂₂ N ₂ O ₃	C,H,N	0.1	-22 ± 3
22	CN	OH	H	CH ₂ C(Me) ₃	O	A	44	174–176	EP	C ₁₈ H ₂₄ N ₂ O ₃	C,H,N	1.0	-36 ± 5
23	CN	OH	H	C ₆ H ₁₁	O	A	31	208–210	EP	C ₁₉ H ₂₈ N ₂ O ₃	C,H,N	0.3	-30 (2)
24	CN	OH	H	C ₆ H ₅	O	A	40	183–185	EP	C ₁₉ H ₁₈ N ₂ O ₃	C,H,N	3.0	-27 ± 4
25	CN	OH	H	4-F-C ₆ H ₄	O	A	60	212–215	EP	C ₁₉ H ₁₇ N ₂ O ₃ ·F·H ₂ O	C,H,N	1.0	-9 ± 3
26	CN	OH	H	3,4-F ₂ -C ₆ H ₃	O	A	35	220–222	EP	C ₁₉ H ₁₆ N ₂ O ₃ F ₂	C,H,N	3.0	-11 ± 4
27	CN	OH	H	2-C ₆ H ₄ N	O	A	20	216–219	EPM	C ₁₉ H ₁₇ N ₃ O ₃	C,H,N	1.0	-20 ± 3
28	CN	OH	H	NHMe	O	B	58	217 dec	C	C ₁₄ H ₁₇ N ₃ O ₃ ·0.5H ₂ O	C,H,N	3.0	-42 ± 4
29	CN	OH	H	NHCH ₂ Me	O	B	19	173–175	EP	C ₁₅ H ₁₉ N ₃ O ₃	C,H,N	1.0	-22 ± 5
30	CN	OH	H	NH(CH ₂) ₂ Me	O	B	32	190–193	EPM	C ₁₆ H ₂₁ N ₃ O ₃	C,H,N	3.0	-37 (1)
31	CN	OH	H	NHCH(Me) ₂	O	B	46	198–200	EPM	C ₁₆ H ₂₁ N ₃ O ₃	C,H,N	1.0	-6 ± 7
32	CN	OH	H	NHCH(Me) ₂	S	B	49	100 dec	MC	C ₁₆ H ₂₁ N ₃ O ₂ S	C,H,N	3.0	-15 ± 5
33	CN	OH	H	NHC(Me) ₃	O	B	39	129–132	C	C ₁₇ H ₂₃ N ₃ O ₃ ·0.5H ₂ O	C,H,N	1.0	-18 ± 0
												0.3	-24 ± 1
												0.1	-8 ± 1
34	CN	OH	H	NH-C ₆ H ₁₁	O	B	21	182–183	C	C ₁₉ H ₂₅ N ₃ O ₃	C,H,N	3.0	-18 ± 3
35	CN	OH	H	N(Me) ₂	O	B	30	210–212	EM	C ₁₆ H ₁₉ N ₃ O ₃	C,H,N	3.0	-13 ± 3
36	Cl	OH	H	NHC(Me) ₃	O	B	40	190–193	EP	C ₁₆ H ₂₃ N ₂ O ₃ Cl	C,H,N	3.0	-32 ± 3
37	CF ₃	OH	H	NHC(Me) ₃	O	B	73	193–195 dec	EP	C ₁₇ H ₂₃ N ₂ O ₃ F ₃	C,H,N	0.3	-10 ± 3
38	CN	H	H	OC(Me) ₃	O	a	71	141–142	EP	C ₁₇ H ₂₂ N ₂ O ₃	C,H,N	1.0	-26 ± 2
												10.0	-22 ± 4
												3.0	-30 ± 4
												0.3	-26 ± 6
39	CN	H	H	NHC(Me) ₃	O	a	55	208–211	EP	C ₁₇ H ₂₃ N ₃ O 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 ₃ O 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 ₂ O 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 = CH₂Cl₂, 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.

NaN₃ (Scheme III) gave exclusively *trans*-azido carbamate 43, which was reduced with 1,3-propanedithiol in methanol²⁰ to 40. Treatment of 14 (R₁ = CN) with BF₃·Et₂O 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 CH₂ 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 previously² 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 NH₂, 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-CF₃ 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. HF₂₅₄ silica gel plates were used for chromatotron chromatography (radial chromatography), and Kieselgel 60 for column chromatography. Anhydrous Na₂SO₄ 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-2H-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-2H-1-benzopyran 11¹ (11 mmol) in dry PhMe (15 mL) at 35–40 °C under N₂. The solution was then stirred at 50 °C for 6 h and cooled to 0 °C, and a 20% solution of Na₂S₂O₅ in H₂O (40 mL) was added. The mixture was stirred vigorously for 18 h, and the layers were separated. The organic layer was washed with H₂O, NaHCO₃ 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 (R₁ = CN): 58%; mp 164–166 °C (EtOAc–petroleum ether); NMR (CDCl₃) 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, NH), 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. (C₁₇H₂₁N₂O₃Cl) 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-2H-1-benzopyran 13 (5 mmol) and K₂CO₃ (7 mmol) in EtOH (100 mL) and H₂O (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 (R₁ = CN): NMR (CDCl₃) 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; C₁₇H₂₀N₂O₃ requires 300.1474. Compound 14 (R₁ = Cl): NMR (CDCl₃) 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 (R₁ = CF₃): NMR (CDCl₃) 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-2H-1-benzopyran-4-ols (15–17). A solution of the appropriate aziridine 14 (2 mmol) in dioxane (20 mL) and 1% H₂SO₄ (20 mL) was stirred at room temperature for 18 h. Solvents were evaporated, and the residue was partitioned between EtOAc and H₂O. 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 (CDCl₃) 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, NH), 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-2H-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-2H-1-benzopyran 15–17 (6 mmol) in dry CH₂Cl₂ (50 mL) at 0 °C under N₂. 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 NaHCO₃ 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 (R₁ = CN): NMR (CDCl₃) 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)-2H-1-benzopyran-4-ol (18). To a solution of amino alcohol 9 (R₁ = CN, 1.0 g, 4.6 mmol) and Et₃N (1 mL) in CH₂Cl₂

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(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 H₂O was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with dilute HCl, H₂O, and brine, dried, filtered, and evaporated to give a solid which was dissolved in dry THF (100 mL) under N₂, and NaH (0.116 g, 80% dispersion, 3.87 mmol) was added. The solution was stirred at 20 °C for 6 days, then H₂O 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 [(CD₃)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 CH₂Cl₂ (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 NaHCO₃ solution, dried, filtered, and evaporated to give the crude amides, which were purified by recrystallization (see Table I). Compound 21: NMR (CDCl₃) 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, NH), 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 CH₂Cl₂ (25 mL) at 0 °C. The solution was allowed to warm to room 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 [(CD₃)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, NH), 5.88 (d, J = 6 Hz, OH), 5.95 (d, J = 9 Hz, NH), 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-2H-1-benzopyran (38). A solution of 11 (R₁ = 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 NH₄OAc (2.08 g, 27 mmol) in H₂O (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 H₂O, 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 (CDCl₃) 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, NH), 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-2H-1-benzopyran (39). Trifluoroacetic acid (5 mL) was added to a stirred solution of 38 (0.5 g, 1.66 mmol) in dry CH₂Cl₂ (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 NaHCO₃ solution, H₂O, and brine, dried, filtered, and evaporated to give crude amine 42 (0.24 g, 72%), which was dissolved in dry CH₂Cl₂ (30 mL). The solution was cooled to 0 °C under N₂, 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 (CDCl₃) 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 D₂O, 2NH), 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-2H-1-benzopyran (43).** Sodium azide (0.79 g, 12.1 mmol) was added to a stirred mixture of 14 (R₁ = CN, 3.32 g, 11 mmol) and NH₄Cl (0.64 g, 12 mmol) in dry DMF (30 mL). The mixture was heated at 60–65 °C for 5 h, then cooled, and H₂O was added. The mixture was extracted with EtOAc, and the combined organic layers were washed with H₂O 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. (C₁₇H₂₁N₅O₃) C, H, N.

***trans*-4-Amino-3-[(*tert*-butoxycarbonyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2H-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 Et₃N (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 Et₂O 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-2H-1-benzopyran (41).** Boron trifluoride etherate (0.1 mL, 0.8 mmol) was added to a stirred solution of 14 (R₁ = 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 (R₁ = CN), 33143-29-2; 13, 130867-12-8; 14 (R₁ = CN), 130867-13-9; 14 (R₁ = Cl), 130867-16-2; 14 (R₁ = CF₃), 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.