Synthesis and Antihypertensive Activity of Pyran Oxygen and Amide Nitrogen Replacement Analogues of the Potassium Channel Activator Cromakalim

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The synthesis and oral antihypertensive activity in conscious spontaneously hypertensive rats of two new series of compounds related to the prototype potassium channel activator cromakalim (1) are described. In the first series, replacement of the benzopyran oxygen atom by nitrogen or methylene led to the 1,2,3,4-tetrahydroquinoline **12** and 1,2,3,4-tetrahydronaphthalene **13**, which were both less active than 1. However, in contrast to the equivalent activity found previously for 1 and its dehydrated analogue **28**, the dihydronaphthalene **27** was found to be more active than **13**. In the second series, replacement of the C(4) amide nitrogen atom in acyclic amides related to cromakalim by methylene gave ketone **16** that was less active than the corresponding amide **15**. However, replacement of the 4-acetonyl substituent in **16** by *N,N*-dimethylacetamido as in compound **22** resulted in a marked enhancement in activity. The compounds described in this paper thus illustrate the importance of the benzopyran oxygen and C(4) substituent on antihypertensive activity in the cromakalim series of potassium channel activators.

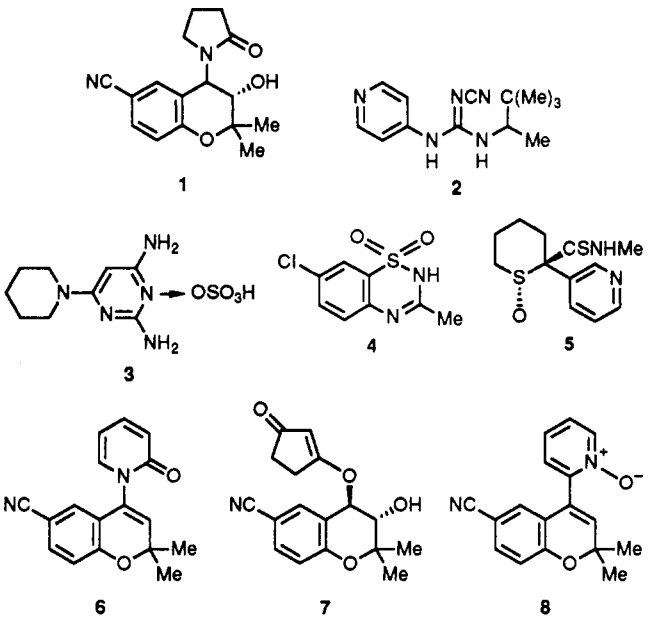
Following the emergence of cromakalim (1),[1,2] the prototype channel activator, other examples of this potentially important class of agent have been reported. Among these (see Chart I) are the established vasodilator pinacidil (2), minoxidil sulfate (3), diazoxide (4), and RP 49356 (5).[3] More recently, potassium channel activators based on the benzopyran nucleus, such as EMD 52692 (6),[4] SDZ PCO 400 (7),[5] and Ro 31-6930 (8),[6] have been disclosed.

In subsequent studies on antihypertensive benzopyran potassium channel activators, we have investigated the effect of incorporation of acyclic amido substituents at C(4)[7] in lieu of the pyrrolidinone group present in compound 1. Furthermore the C(6) electron-withdrawing group has been replaced by alkyl substituents,[8] and the benzopyran nucleus has been replaced by the pyrano-[3,2-*c*]pyridine nucleus.[8]

Besides providing active antihypertensive agents,[1,7,8] it has been established that potassium channel activators have potential use in the treatment of bronchial asthma, and certain analogues described previously[1,8] have been shown[9] by our colleagues to be potent relaxants of guinea pig tracheal tissue.

As part of our continuing study on structural modification of compound 1 and related acyclic amides, it was decided to investigate the effect on antihypertensive activity of replacing the pyran oxygen atom by a carbon or a nitrogen atom, and the nitrogen atom at C(4) by a carbon atom. Hence this paper describes the synthesis of a series of 2,2-dimethyl-1,2,3,4-tetrahydroquinolines, -naphthalenes, and their dihydro derivatives, and benzopyrans containing substituents at C(4) linked by carbon and their evaluation in the spontaneously hypertensive rat (SHR) in comparison with compound 1. Also included in Table I are compounds **15**, **18**, **20**, and **28**, which have been reported in our earlier publications,[7,8] that provide a more meaningful comparison of activities, being structurally closer than compound 1 to certain of the compounds described in this study.

Chart I



Chemistry

Although the 6-chloro- (**29**) and 6-bromo-2,2-dimethyl-1,2-dihydroquinolines (**30**, Scheme I) were readily prepared following the literature[10] procedure, the 6-cyano analogue **31** could not be prepared using this method. Consequently the synthetic approach relied on halogen replacement during the ultimate stage. The dihydroquinolines **29** and **30** could not be directly epoxidized with *m*-chloroperbenzoic acid or hydrobrominated with aqueous NBS. However, *N*-acetylation of compounds **29** and **30**

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(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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(4) Bergmann, R.; Gericke, R. Synthesis and Antihypertensive Activity of 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2*H*-1-benzopyrans and Related Compounds, New Potassium Channel Activators. *J. Med. Chem.* **1990**, *33*, 492-503.
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(6) Paciorek, P. M.; Burden, D. T.; Burke, Y. M.; Cowlrick, I.; Perkins, R. S.; Taylor, J. C.; Waterfall, J. F. Preclinical Pharmacology of Ro 31-6930, a New Potassium Channel Opener. *J. Cardiovasc. Pharmacol.* **1990**, *15*, 188-192.
(7) Ashwood, V. A.; Cassidy, F.; Coldwell, M. C.; Evans, J. M.; Hamilton, T. C.; Howlett, D. R.; Smith, D. M.; Stemp, G. Synthesis and Antihypertensive Activity of 4-(Substituted-carbonylamino)-2*H*-1-benzopyrans. *J. Med. Chem.* **1990**, *33*, 2667-2672.

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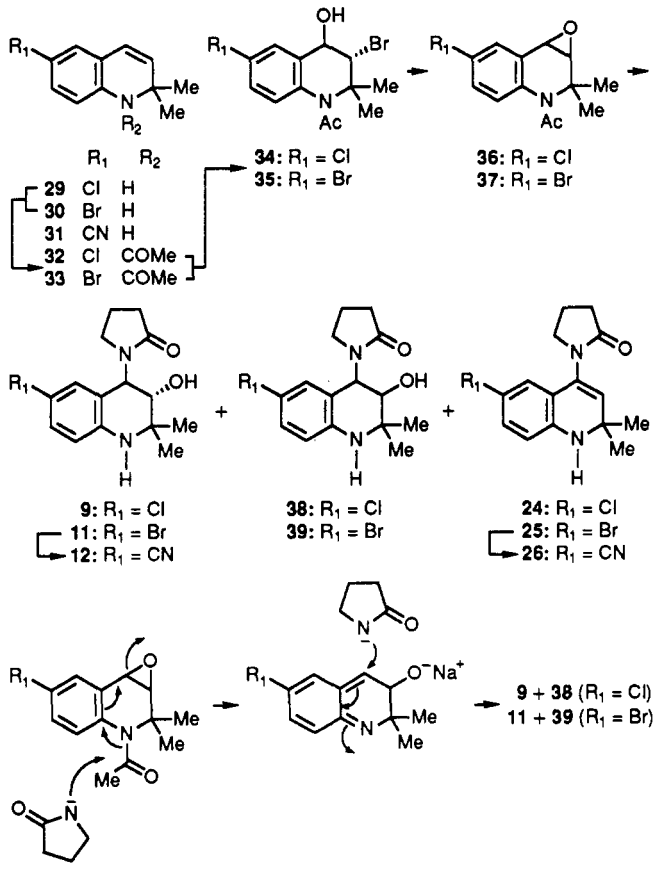
Scheme I

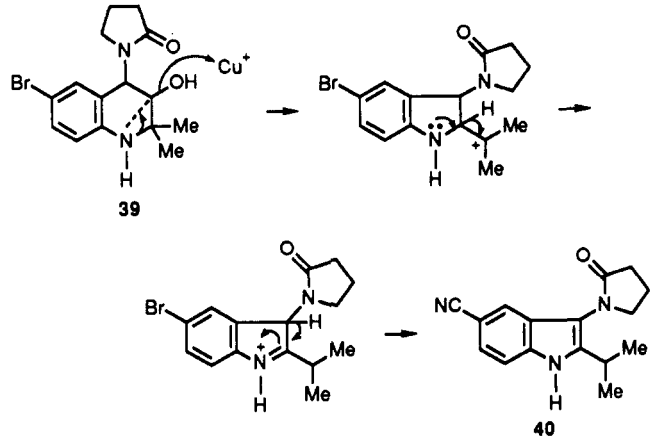


gave compounds **32** and **33**, respectively, which underwent the hydrobromination reaction with moist NBS to yield compounds **34** and **35**, respectively. Basic treatment of the bromohydrins furnished the epoxides **36** and **37**, respectively (Scheme I).

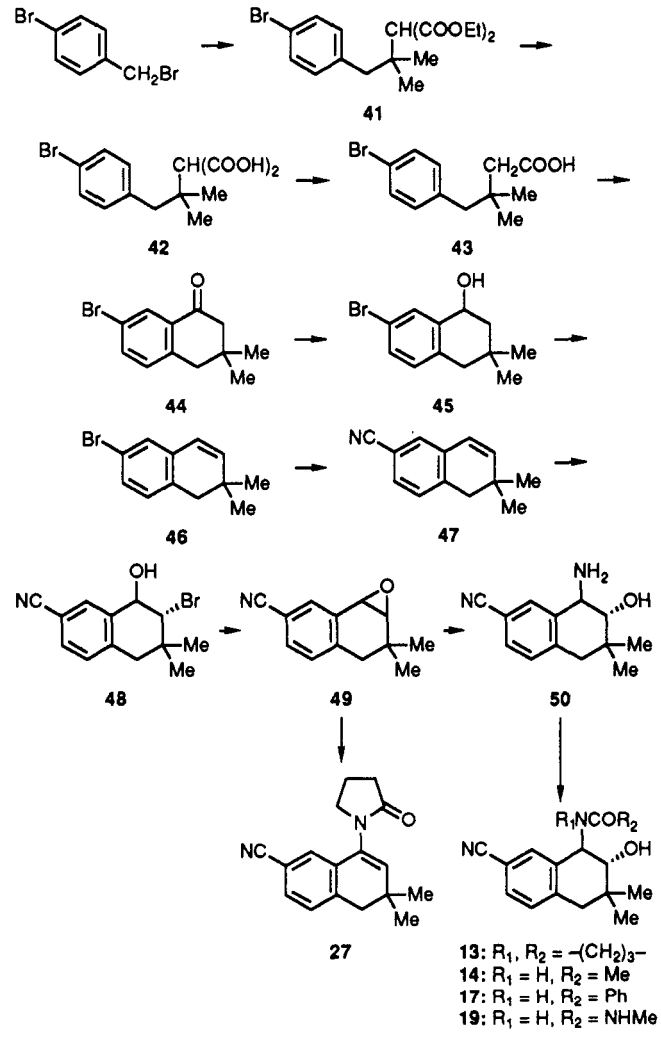
Reaction of the 6-chloro epoxide **36** with the anion of 2-pyrrolidinone in DMSO gave a mixture of the *cis*- and *trans*-tetrahydroquinolines **38** and **9**, respectively, and the dihydroquinoline **24**. Similarly, the 6-bromo epoxide **37** gave the *cis*- and *trans*-tetrahydroquinolines, **39** and **11**, respectively, and the dihydroquinoline **25**. In each case the *N*-acetyl group was removed during the reaction. A probable explanation for the formation of cis and trans products in these reactions is via the mechanism shown in Scheme I, involving initial attack on the *N*-acetyl group and formation of a planar intermediate, which is supported by data on closely related compounds.[11]

The *trans*-6-bromotetrahydroquinoline **11** and the dihydroquinoline **25** were both converted to the C(6)-cyano analogues **12** and **26**, respectively, on treatment with an excess of Cu(I)CN in *N*-methylpyrrolidinone (NMP). Interestingly, under similar conditions, the *cis*-tetrahydroquinoline **39** product rearranged to give the indole **40** as

Scheme II



Scheme III



the sole product (65%), possibly by the process depicted in Scheme II.

Synthesis of the tetrahydronaphthalene analogues employed 4-bromobenzyl bromide as starting material (Scheme III). Formation of the Grignard reagent and reaction with diethyl isopropylidenemalonate gave the bromophenyl malonate **41**. A standard basic hydrolysis furnished the diacid **42**, which was thermally decarboxylated to the butanoic acid derivative **43**. Ring closure was accomplished with phosphoric acid at 100 °C to give 7-bromodihydronaphthalen-1-one **44**, which in turn was reduced to the alcohol **45** with borohydride. Elimination of

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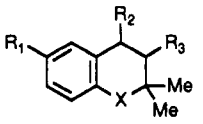
(11) Evans, J. M.; Gagliardi, S.; Stemp, G. Unpublished results.

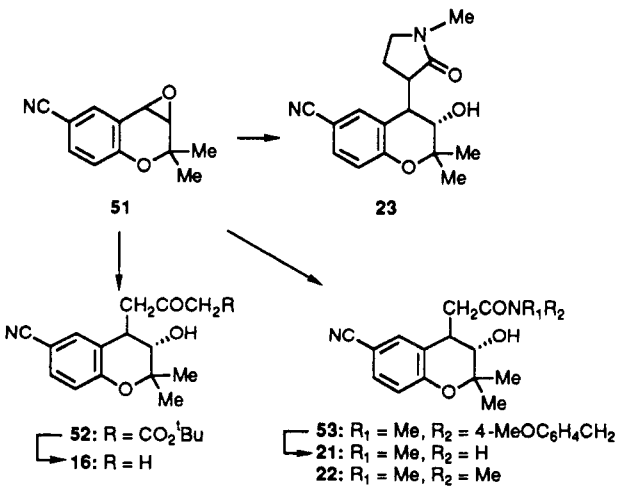
Table I. Pyran Oxygen and C(4) Nitrogen Replacement Analogues of Cromakalim (1)



no.	R_1	R_2	R_3	X	yield, %	mp, °C	recryst solvent[a]	formula	anal.[b]	dose, mg/kg	max fall[c] in bp, % ± SEM
1[d]	CN	c-NCO(CH$_2$)$_3$	OH	O						0.3	39 ± 4
										1.0	47 ± 1
9	Cl	c-NCO(CH$_2$)$_3$	OH	NH	19	82–85	E-P	$C_{15}H_{19}N_2O_2Cl$	C,H;N[e]	10.0	8 ± 3
10[d]	Cl	c-NCO(CH$_2$)$_3$	OH	O						10.0	37 ± 7
11	Br	c-NCO(CH$_2$)$_3$	OH	NH	30	93–102	C	$C_{15}H_{19}N_2O_2Br$	M$^+$/	10.0	6 ± 3
12	CN	c-NCO(CH$_2$)$_3$	OH	NH	25	297–298	E	$C_{16}H_{19}N_3O_2$	C,H,N	1.0	9 ± 5
										3.0	26 ± 5
										10.0	39 (n = 2)
13	CN	c-NCO(CH$_2$)$_3$	OH	CH$_2$	53	203–204	E	$C_{17}H_{20}N_2O_2$	C,H,N	3.0	29 ± 2
										10.0	32 ± 4
14	CN	NHCOMe	OH	CH$_2$	35	203–205	E-P	$C_{15}H_{18}N_2O_2$	C,H,N	1.0	22 ± 2
										3.0	34 ± 4
15[g]	CN	NHCOMe	OH	O					C,H,N	0.1	18 ± 2
										0.3	47 ± 5
										1.0	67 ± 4
16	CN	CH$_2$COMe	OH	O	19	114–115	E-P	$C_{15}H_{17}NO_3$	C,H,N	1.0	5 ± 4
										10.0	30 ± 6
17	CN	NHCOPh	OH	CH$_2$	70	205–207	E-PE	$C_{20}H_{20}N_2O_2$	C,H,N	3.0	16 ± 4
										10.0	44 ● 3
18	CN	NHCOPh	OH	O						0.3	16 ± 3
										1.0	41 ± 8
19	CN	NHCONHMe	OH	CH$_2$	68	209.5–211	E-M	$C_{15}H_{19}N_3O_3$	C,H,N	3.0	23 ± 2
										10.0	52 ± 2
20[g]	CN	NHCONHMe	OH	O						0.3	31 ± 9
										1.0	61 ± 3
21	CN	CH$_2$CONHMe	OH	O	10	141–142	E	$C_{15}H_{18}N_2O_3$	C,H,N	3.0	9 ± 6
22	CN	CH$_2$CONMe$_2$	OH	O	24	174–175	E-PE	$C_{16}H_{20}N_2O_3$	C,H,N	1.0	28 ± 4
										3.0	51 ± 3
23	CN	c-CHCONMe(CH$_2$)$_2$	OH	O	20	236–237	E-PE	$C_{17}H_{20}N_2O_3$	C,H,N	3.0	10 ± 2
										10.0	21 ± 3
24	Cl	c-NCO(CH$_2$)$_3$	$\Delta^{3,4}$	NH	45	158–159	E-PE	$C_{15}H_{17}N_2OCl$	C,H,N	10.0	13 ± 2
25	Br	c-NCO(CH$_2$)$_3$	$\Delta^{3,4}$	NH	15	177–178	E-P	$C_{15}H_{17}N_2OBr$	C,H,N	10.0	4 ± 1
26	CN	c-NCO(CH$_2$)$_3$	$\Delta^{3,4}$	NH	50	207–209	E-P	$C_{16}H_{17}N_{30}O$	C,H,N	1.0	10 ± 3
										3.0	29 ± 4
										10.0	49 ● 4
27	CN	c-NCO(CH$_2$)$_3$	$\Delta^{3,4}$	CH$_2$	19	131–132	E-P	$C_{17}H_{18}N_2O$	C,H,N	1.0	23 ± 6
										3.0	50 ± 2
28[d]	CN	c-NCO(CH$_2$)$_3$	$\Delta^{3,4}$	O			E-PE			0.1	12 ± 3
										0.3	47 ± 5

[a] C = chromatography, E = EtOAc, PE = 60–80 °C petroleum ether, P = pentane. [b] Analysis for the elements indicated were within ±0.4% of the theoretical values. [c] Systolic blood pressure was measured indirectly at intervals from 1 to 6 h in groups of six SH rats per dose level, unless indicated. [d] See ref 1. [e] N: calcd, 9.52; found, 8.96. [f] Mass ($C_{15}H_{10}N_2O_2Br$) found m/z 338.0639, calcd 338.0630. [g] See ref 7.

Scheme IV



water from alcohol **45** gave the bromodihydronaphthalene **46**, which was converted to the 7-cyano analogue **47** using Cu(I)CN in refluxing NMP. Compound **47** was then subjected to our usual procedure,[1] giving the epoxide **49** via the bromohydrin **48**. However, unlike the formation of compound **1** from its precursor epoxide **51**,[7] problems were encountered when the same conditions were applied to epoxide **49**, as treatment with pyrrolidin-2-one anion resulted in the formation of the 3,4-dihydronaphthalene **27**. Hence formation of the desired analogue **13** of compound **1** required the preparation of the amino alcohol **50**, followed by acylation with chlorobutyryl chloride and ring closure under basic conditions. Amino alcohol **50** was acylated with acetyl chloride and benzoyl chloride to give the acetylamino (**14**) and benzoylamino (**17**) analogues, respectively, while reaction with methyl isocyanate yielded the methylurea **19**.

Epoxide **51** (Scheme IV) was treated with the dilithium anion of *tert*-butyl acetoacetate using a literature procedure[12] to give the butyrate **52**. Hydrolysis and decarboxylation provided the methyl ketone **16**. In order to prepare

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the C(4) carbon analogue 21 of urea 20,[7] epoxide 51 was treated with *N*-methyl-*N*-(4-methoxybenzyl)acetamide and lithium diisopropylamide generated in situ, and the resulting compound 53 was debenzylated by treatment with methanesulfonic acid during 6 days to give the requisite compound 21. The *N,N*-dimethyl compound 22 was obtained directly from epoxide 51 by the action of *N,N*-dimethylacetamide, again using lithium diisopropylamide as the base, and a similar reaction using NMP gave the cyclic analogue 23.

Results and Discussion

The compounds of Table I were evaluated for oral antihypertensive activity in the 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 occurred between 1 and 4 h postdose, with some recovery to the predose level of blood pressure being observed at 6 h.

The replacement of the pyran oxygen atom, both by the nitrogen atom and methylene group as in compounds 12 and 13, respectively, furnished compounds of approximately equal activity to each other, both being approximately 10-fold less active than cromakalim 1.[1] The chloro (9) and bromo (11) analogues demonstrated little activity at the top dose investigated in this study, unlike the corresponding chlorobenzopyran compound 10.[1] It has been shown[7] that the C(4)-acetylamino substituent, as in compound 15 conferred high activity in the benzopyran series, being slightly more active than the C(4)-pyrrolidinone substituent, as in compound 1. In the tetrahydronaphthalene series the acetylamino compound 14 showed similar activity to that of the pyrrolidinone compound 13. However, the general trend of reduced activity in the tetrahydronaphthalene series compared with the benzopyran series is exemplified by acetylamino compound 14, benzamide 17, and methylurea 19, which are up to 1 order of magnitude less active than their benzopyran counterparts 15, 18, and 20, respectively.

Of the dihydroquinolines, the C(6)-halogenated compounds 24 and 25 were only slightly active at 10 mg/kg. In contrast the C(6)-cyano compound 26 showed enhanced activity, presumably due to the presence of the stronger electron withdrawing substituent, but was much less active than the benzopyran analogue 28. Although in general the tetrahydroquinoline and -naphthalene series were comparable in activity, an exception was noted in the dihydronaphthalene 27, which was approximately twice as active as the corresponding dihydroquinoline 26, but again was less active than the benzopyran 28. It is noteworthy that dihydronaphthalene 27 is approximately twice as active as tetrahydronaphthalene 13, in contrast to the similar activities observed for the corresponding benzopyrans 28 and 1.

In replacement of the nitrogen atom at C(4) by a methylene unit, the ketone 16 and amides 21 and 23 were all very much less active than their corresponding C(4) analogues 15, 20, and 1, respectively. Presumably the tetrahedral nature of the carbon atom attached to C(4) in the analogues 16, 21, and 23 alters the configuration of the ubiquitous carbonyl group by moving the substituent out of the orthogonal disposition with respect to the benzopyran nucleus that we have commented on previously.[13]

Interestingly, amide 22 with a second N-methyl group is markedly more active than amide 21. One can speculate that the additional methyl group increases the probability of the amide group adopting the optimal conformation for activity.

In the series of compounds presented here, it can be seen that replacement of either the pyran oxygen atom by a nitrogen atom or a methylene group or the C(4) nitrogen atom by a methylene group, provides compounds that, in general, are less active as antihypertensive agents in the SHR. Nevertheless, this study has provided compounds (22 and 27) that are comparable in activity to many of the compounds reported previously,[1,7,8] together with compound 12, which has been shown to have potential for the treatment of cerebrovascular disorders.[14] It also illustrates the importance of two further features, namely the pyran oxygen atom and the nature of C(4) substituent, in conferring optimal antihypertensive activity in the cromakalim series of potassium channel activators.

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 for IR, a Varian EM 360A at 60 MHz, a Varian CFT-20 at 80 MHz, or a JEOL GX 270 for NMR, and a VG70-70 or 70 ZAB at 70 eV for mass spectra, 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.

6-Chloro- and 6-Bromo-2,2-dimethyl-1,2-dihydroquinoline (29 and 30, Respectively). The compounds were prepared from the corresponding anilines following the literature[10] methods A and C, with that of compound 30 employing Cu(I)Br.

Compound 29: 36%; bp 85–100 °C (0.06 mmHg); NMR ($CDCl_3$) δ 1.25 [s, 6 H, $C(Me)_2$], 3.45 (s, NH), 5.35 (d, 9, H-3), 6.10 (d, 9, H-4), 6.20 (d, 10, H-8), 6.70 (m, H-5 and H-7); mass spectrum ($C_{11}H_{12}NCl$) found m/z 193.0658, calcd 193.0658.

Compound 30: 33%; bp 90–102 °C (0.03 mmHg); mass spectrum ($C_{11}H_{12}NBr$) found m/z 237.0152, calcd 237.0154.

1-Acetyl-6-chloro- and 1-Acetyl-6-bromo-2,2-dimethyl-1,2-dihydroquinoline (32 and 33, Respectively). Acetyl chloride (12 mL, 0.083 mol) was added dropwise to a stirred solution of compound 29 (16 g, 0.083 mol) and *N,N*-diethylaniline (24 mL, 0.19 mol) in CH_2Cl_2 (200 mL) at 0 °C. The solution was stirred at room temperature for an additional 24 h and then poured into H_2O, and the organic layer was separated. The organic layer was washed with 1 N HCl, 5% $NaHCO_3$ solution, H_2O, and brine and dried. Filtration and evaporation gave the crude *N*-acetyl derivative 32 as a brown gum (18.9 g, 97%): NMR ($CDCl_3$) δ 1.50 [s, 6 H, $C(Me)_2$], 2.10 (s, 3 H, NCOMe), 5.60 (d, 10, H-3), 6.15 (d, 10, H-4), 6.60 (d, 8, H-8), 6.90 (m, H-5 and H-7); mass spectrum ($C_{13}H_{14}CINO$) found m/z 235.0766, calcd 235.0764.

Compound 33 was prepared in a similar manner as a pale yellow oil: 96%; NMR ($CDCl_3$) δ 1.50 [s, 6 H, $C(Me)_2$], 2.12 (s, 3 H, COMe), 5.61 (d, 10, H-3), 6.17 (d, 10, H-4), 6.57 (d, 8, H-8), 7.03 (narrow m, H-5) overlapping 7.11 (q, 8, 2, H-7).

***trans*-1-Acetyl-3-bromo-6-chloro-2,2-dimethyl-1,2,3,4-tetrahydroquinolin-4-ol (34) and *trans*-1-Acetyl-3,6-dibromo-2,2-dimethyl-1,2,3,4-tetrahydroquinolin-4-ol (35).** NBS (16.0 g, 0.09 mol) was added to a vigorously stirred solution of compound 32 (18.9 g, 0.08 mol) in DMSO (150 mL) and H_2O (15 mL, 0.83 mol). The mixture was stirred for 1 h at room temperature and then diluted with H_2O and extracted with EtOAc. The organic extracts were washed with H_2O and brine and dried. Filtration and evaporation gave the bromohydrin 34 as a dark brown gum (26.5 g, 99%): mass spectrum ($C_{13}H_{15}BrClNO_2$) found

(13) Cassidy, F.; Evans, J. M.; Smith, D. M.; Stemp, G.; Edge, C.; Williams, D. J. Conformational Analysis of the Novel Antihypertensive Agent Cromakalim (BRL 34915). *J. Chem. Soc., Chem. Commun.* **1989**, 377–378.

(14) Angersbach, D.; Evans, J. M.; Nicholson, C. D.; Stemp, G. U.S. Pat. Appl. US 4,808,619, 1989.

m/z 374.9476, calcd 374.9471.

Similarly prepared was compound **35** (93%) as a black gum: NMR ($CDCl_3$) δ 1.68 [s, 6 H, $C(Me)_2$], 2.08 (s, 3 H, NCOMe), 3.79 (d, 9, H-3), 4.70 (d, 9, H-4), 6.70 (d, 8, H-8), 7.27 (q, 8, 2, H-7), 7.60 (narrow m, H-5); IR (film) 3310, 1660 cm^{-1}; mass spectrum ($C_{13}H_{15}NO_2Br_2$) found m/z 374.9476, calcd 374.9471.

1-Acetyl-6-chloro- and 1-Acetyl-6-bromo-2,2-dimethyl-3,4-epoxy-1,2,3,4-tetrahydroquinoline (36 and 37, Respectively). A mixture of compound **34** (26.5 g, 0.08 mol) and KOH pellets (25 g, 0.45 mol) in dry Et_2O (500 mL) was stirred vigorously at room temperature for 48 h. Filtration and evaporation gave epoxide **36** (18.5 g, 92%) as a dark colored gum which was used directly in the next stage: NMR ($CDCl_3$) δ 1.20 (s, 3 H, Me), 1.85 (s, 3 H, Me), 2.10 (s, 3 H, COMe), 3.35 (d, 4, H-3), 3.75 (d, 4, H-4), 6.65 (d, 9, H-8), 7.15 (m, H-5 and H-7).

Similarly prepared was compound **37** (83%) as a dark green gum: mass spectrum ($C_{13}H_{14}NO_2Br$) found m/z 295.0217, calcd 295.0208.

***cis*- and *trans*-6-Chloro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-1,2,3,4-tetrahydroquinolin-3-ols (38 and 9, Respectively) and 6-Chloro-2,2-dimethyl-4-(2-oxopyrrolidinyl)-1,2-dihydroquinoline (24).** Pyrrolidin-2-one (1.28 g, 15 mmol) was added to a suspension of NaH (0.52 g of 80% oil dispersion, 17 mmol) in DMSO (100 mL) under N_2, and the mixture was stirred for 10 min. A solution of epoxide **36** (3.6 g, 15 mmol) in DMSO (10 mL) was added to the solution, which was stirred at room temperature for 4 h. Water was added cautiously to the reaction mixture, which was extracted with EtOAc. The organic layer was washed with brine and dried. Filtration and evaporation gave a crude product which was chromatographed on silica gel. Elution with 5% MeOH–CH_2Cl_2 gave compound **24** (0.4 g; see Table I), followed by compound **38** (0.8 g, 19%) and compound **9** (0.8; see Table I). **38**: mp 64–65 °C as the hemihydrate; NMR ($CDCl_3$) δ 1.20 [s, 6 H, $C(Me)_2$], 2.05 (m, 3 H, NCH_2CH_2 and NH), 2.50 (m, 2 H, $COCH_2$), 3.55 (m, NCH_2 and H-4), 5.45 (d, 3.5, H-4), 6.50–7.10 (m, 3 ArH). Anal. ($C_{15}H_{19}N_2O_2Cl \cdot 0.5H_2O$) C, H, N. The remaining fractions contained starting epoxide **36** (>40%).

Similarly prepared were the 6-bromo analogues **11**, **25** (see Table I), and the cis compound **39**. **39**: a yellow solid; mp 76–80 °C; NMR ($CDCl_3$) δ 1.25 [s, 6 H, $C(Me)_2$], 2.05 (m, 2 H, NCH_2CH_2), 2.25 (d, 10, OH), 2.50 (m, 2 H, $COCH_2$), 3.30 (m, 1 H, NCH_2), 3.60 (m, 1 H, NCH_2), 3.65 (q, 10, 4, collapsing to d, 4, on addition of D_2O H-3), 3.80 (m, NH), 5.45 (d, 4, H-4), 6.45 (d, 8, H-8), 7.10 (m, H-5 and H-7); mass spectrum ($C_{15}H_{19}N_2O_2Br$) found m/z 338.0635, calcd 338.0603.

***trans*-6-Cyano-2,2-dimethyl-4-(2-oxopyrrolidinyl)-1,2,3,4-tetrahydroquinolin-3-ol (12).** A solution of compound **11** (0.37 g, 1.1 mmol) and Cu(I)CN (0.2 g, 2.2 mmol) in NMP (10 mL) was refluxed for 4 h. The mixture was cooled and poured into 10% aqueous ethylenediamine and extracted with EtOAc. The organic phase was washed with H_2O, and dried. Filtration and evaporation gave compound **12** as white microcrystals (76 mg; see Table I).

5-Cyano-3-(2-oxopyrrolidinyl)-2-isopropylindole (40). A solution of compound **39** (0.5 g, 1.5 mmol) and Cu(I)CN (0.25 g, 2.8 mmol) in NMP (25 mL) was refluxed for 4 h. The solution was cooled and poured into 10% aqueous ethylenediamine and extracted with EtOAc. The organic phase was washed with 10% aqueous ethylenediamine and dried. Filtration and evaporation gave a gum which was radially chromatographed using a gradient elution from EtOAc–pentane to EtOAc. The product was recrystallized from EtOAc–pentane to give compound **40** (0.26 g, 65%): mp 249–250 °C; NMR ($CDCl_3$) δ 1.22 [d, 7, 6 H, $C(Me)_2$], 2.35 (m, 2 H, NCH_2CH_2), 2.65 (m, 2 H, $COCH_2$), 3.05 [sp, 7, 1 H, $CH(Me)_2$], 3.77 (t, 7, 2 H, NCH_2), 7.30 (m, H-6 and H-7), 7.70 (d, 1.5, H-4), 9.05 (m, NH). Anal. ($C_{16}H_{17}N_3O$) C, H, N.

Diethyl [2-(4-Bromophenyl)-1,1-dimethylethyl]malonate (41). A solution of *p*-bromobenzyl bromide (25 g, 0.1 mol) in dry Et_2O (200 mL) was added dropwise to a suspension of Mg turnings (2.4 g, 0.1 mol), under N_2, at such a rate as to maintain reflux. The mixture was refluxed for an additional 1.5 h and cooled to 0 °C. Cu(I)Cl (0.2 g, 2 mmol) was added to the solution which was vigorously stirred for 5 min. A solution of diethyl isopropylidenemalonate (15 g, 74 mmol) in Et_2O (50 mL) was added dropwise to the reaction mixture, with cooling to 0–5 °C. The mixture was allowed to attain room temperature with stirring during 1 h and then poured into dilute H_2SO_4. The layers were separated, and the aqueous phase was extracted with Et_2O. The ether extract was washed with $NaHCO_3$ solution, H_2O, and brine and dried. Filtration, evaporation, and chromatography on silica gel using 10% Et_2O–petroleum ether gave compound **41** as an oil (17.0 g, 46%): NMR ($CDCl_3$) δ 1.10 [s, 6 H, $C(Me)_2$], 1.25 (t, 6 H, CH_2CH_3), 2.75 (s, 2 H, $PhCH_2$), 3.20 (s, CH), 4.15 (q, 4 H, CH_2CH_3), 6.90 (d, 8, 2 ArH), 7.25 (d, 8, 2 ArH).

[2-(4-Bromophenyl)-1,1-dimethylethyl]malonic Acid (42). A solution of compound **41** (17 g, 0.046 mmol) and KOH (17 g, 0.31 mol) in EtOH (100 mL) and H_2O (50 mL) was stirred at room temperature for 48 h. The solution was diluted with H_2O and extracted with EtOAc. Drying and removal of solvent and recrystallization from Me_2CO–petroleum ether gave the diacid **42** (8.0 g, 55%) with mp 169–173 °C: $C_{13}H_{15}BrO_4$ (C, H).

4-(4-Bromophenyl)-3,3-dimethylbutanoic Acid (43). Compound **42** (10.9 g, 0.035 mmol) was heated in an oil bath at 200 °C for 0.5 h to give the butanoic acid **43** (9.3 g, 99%). A small sample, recrystallized from 60–80 °C petroleum ether had mp 81–83 °C: mass spectrum ($C_{12}H_{15}BrO_2$) found m/z 270.0261, calcd 270.0256.

7-Bromo-3,3-dimethyl-3,4-dihydro-1(2*H*)-naphthalenone (44). A mixture of compound **43** (9.2 g, 34 mmol) and polyphosphoric acid (100 mL) was heated at 100 °C, with occasional swirling for 1 h. The solution was cooled, and H_2O (400 mL) was added cautiously. The solution was extracted with EtOAc, and the organic phase was washed with H_2O and brine and dried. Filtration and evaporation gave compound **44** (8.2 g, 95%) as a gum: NMR ($CDCl_3$) δ 1.05 [s, 6 H, $C(Me)_2$], 2.45 (s, 2 H, H-2), 2.75 (s, 2 H, H-4), 7.00 (d, 8, H-5), 7.45 (q, 8, 2, H-6), 8.05 (d, 2, H-8); mass spectrum ($C_{12}H_{13}BrO$) found m/z 252.0171, calcd 252.0150.

7-Bromo-3,3-dimethyl-1,2,3,4-tetrahydro-1-naphthol (45). A solution of compound **44** (7.8 g, 31 mmol) in dry EtOH (50 mL) at 0 °C was treated with $NaBH_4$ (1.5 g, 47 mmol). The mixture was stirred and allowed to attain room temperature during 18 h. Evaporation and partition of the residue between EtOAc and H_2O and drying and evaporation of the organic layer gave compound **45** (7.0 g, 89%): NMR ($CDCl_3$) δ 1.00 [s, 3 H, $C(Me)_2$], 1.20 [s, 3 H, $C(Me)_2$], 1.35–2.10 (m, 2 H, H-2), 2.20 (s, OH), 2.50 (s, 2 H, H-4), 4.80 (m, H-1), 6.90 (d, 8, H-5), 7.20 (q, 8, 3, H-6), 7.65 (d, 3, H-8); mass spectrum ($C_{12}H_{15}OBr$) found m/z 254.0310, calcd 254.0307.

7-Bromo-3,3-dimethyl-3,4-dihydronaphthalene (46). A solution of compound **45** (7.0 g, 28 mmol) and *p*-toluenesulfonic acid (0.5 g, 3 mmol) in PhH (100 mL) was refluxed for 1.5 h using a Dean–Stark H_2O separator. The solution was cooled, evaporated, and partitioned between Et_2O and H_2O. The organic layer was washed with $NaHCO_3$ solution, H_2O, and brine and dried. Filtration and evaporation gave compound **46** (6.2 g, 95%) as an oil: NMR ($CDCl_3$) δ 1.00 [s, 3 H, $C(Me)_2$], 2.55 [s, 3 H, $C(Me)_2$], 5.75 (d, 9, H-2), 6.20 (d, 9, H-1), 6.80–7.40 (m, 3 ArH); mass spectrum ($C_{12}H_{13}Br$) found m/z 236.0209, calcd 236.0201.

7-Cyano-3,3-dimethyl-3,4-dihydronaphthalene (47). A solution of compound **46** (6.2 g, 26 mmol) and Cu(I)CN (3.5 g, 39 mmol) in NMP (60 mL) was refluxed for 2 h. The solution was cooled and poured into 10% aqueous ethylenediamine (200 mL) and extracted with EtOAc. The organic layer was washed with H_2O and dried. Filtration and evaporation and chromatography on silica gel using 10% Et_2O–pentane as eluent gave compound **47** (4.6 g, 96%) as a crystalline solid with mp 50–52 °C. Anal. ($C_{13}H_{13}N$) C, H, N.

2-Bromo-7-cyano-3,3-dimethyl-1,2,3,4-tetrahydro-1-naphthol (48). NBS (5.0 g, 28 mmol) was added to a vigorously stirred solution of compound **47** (4.5 g, 25 mmol) in DMSO (50 mL) and H_2O (4 mL, 0.2 mol). The mixture was stirred at room temperature for 1 h, diluted with H_2O, and extracted with EtOAc. The organic extract was washed with H_2O and brine and dried. Filtration and evaporation gave the bromohydrin **48** as a colorless solid (7.0 g, 99%). A small portion, recrystallized from EtOAc, had a melting point of 164–165 °C. Anal. ($C_{13}H_{14}NOBr$) C, H, N.

7-Cyano-1,2-epoxy-3,3-dimethyl-1,2,3,4-tetrahydronaphthalene (49). A mixture of bromohydrin **48** (6.9 g, 25 mmol) and KOH pellets (15 g, 0.27 mol) in dry Et_2O (1 L) was vigorously stirred at room temperature for 48 h. Filtration and evaporation

gave the epoxide **49** (4.5 g, 91%) as a gum which was used directly without purification: NMR ($CDCl_3$) δ 0.85 [s, 3 H, $C(Me)_2$], 1.35 [s, 3 H, $C(Me)_2$], 2.20 (q, 15, 2, 1 H, CH_2), 2.70 (d, 15, 1 H, CH_2), 3.20 (q, 4, 2, H-2), 3.75 (d, 4, H-1), 7.05 (d, 8, H-5), 7.57 (m, H-6 and H-8).

***trans*-1-Amino-7-cyano-3,3-dimethyl-1,2,3,4-tetrahydro-2-naphthol (50).** A solution of compound **49** (3.5 g, 18.6 mmol) in EtOH (50 mL) and NH_4OH solution (100 mL, 0.88) was stirred at room temperature for 10 days. EtOAc (50 mL) was added to the solution and the mixture extracted with dilute HCl. The acidic extracts were made basic with NaOH solution and extracted with EtOAc. The organic extract was washed with H_2O and brine and dried. Filtration and evaporation gave compound **50** as a solid (2.0 g, 53%) with mp 104–106 °C: mass spectrum ($C_{13}H_{16}N_2O$) found m/z 216.1279, calcd 216.1263.

***trans*-7-Cyano-3,3-dimethyl-1-(2-oxopyrrolidinyl)-1,2,3,4-tetrahydro-2-naphthol (13).** A solution of amino alcohol **50** (0.5 g, 2.3 mmol), Et_3N (0.5 mL, 3.5 mmol), and 4-chlorobutyryl chloride (0.33 g, 2.3 mmol) in CH_2Cl_2 (35 mL) was stirred at room temperature for 1 h. The solution was poured into dilute HCl, and the organic layer was separated and washed with Na_2CO_3 solution and dried. Filtration and evaporation gave the crude amide (0.8 g) which was dissolved in dry THF (60 mL). To this solution was added 80% NaH (75 mg, 2.5 mmol), under N_2. The mixture was stirred at room temperature for 1.5 h, and then poured cautiously into H_2O and extracted with EtOAc. The organic extract was washed with brine and dried. Filtration, evaporation, and recrystallization gave compound **13** (0.35 g; see Table I): NMR ($CDCl_3$) δ 0.95 [s, 3 H, $C(Me)_2$], 1.20 [s, 3 H, $C(Me)_2$], 1.95–2.30 (m, 2 H, NCH_2CH_2), 2.45 (br s, OH), 2.50–2.80 (m, 4 H, $PhCH_2$ and $COCH_2$), 2.85–3.50 (m, 2 H, NCH_2), 3.70 (d, 10, H-2), 5.25 (d, 10, H-1), 7.15–7.55 (m, 3 ArH).

***trans*-1-(Acetylamino)-7-cyano-3,3-dimethyl-1,2,3,4-tetrahydro-2-naphthol (14).** Acetyl chloride (0.17 mL, 2.4 mmol) was added to a stirred solution of amino alcohol **50** (0.52 g, 2.4 mmol) and Et_3N (0.5 mL, 3.5 mmol) in CH_2Cl_2 (75 mL). The reaction mixture was allowed to stand for 36 h at room temperature. Water was added to the solution and the organic layer separated. The organic extract was washed with 2 N HCl, Na_2CO_3 solution, H_2O, and brine and dried. Filtration, evaporation, and recrystallization of the residue gave compound **14** (0.22 g) as colorless microcrystals (see Table I).

***trans*-1-(Benzoylamino)-7-cyano-3,3-dimethyl-1,2,3,4-tetrahydro-2-naphthol (17).** A solution of amino alcohol **50** (0.22 g, 1.02 mmol), Et_3N (0.4 mL, 2.8 mmol), and PhCOCl (0.145 g, 1.03 mmol) in CH_2Cl_2 (30 mL) was maintained at room temperature for 18 h. The solution was poured into dilute HCl, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2, and the combined organic extract was washed with Na_2CO_3 solution and dried. Filtration, evaporation, and recrystallization gave compound **17** (230 mg) as colorless needles (see Table I).

***trans*-7-Cyano-3,3-dimethyl-1-(*N*,*N*'-methylureido)-1,2,3,4-tetrahydro-2-naphthol (19).** MeNCO (60 mg, 1.05 mmol) was added to a solution of amino alcohol **50** (0.22 g, 1.02 mmol) in CH_2Cl_2 (20 mL). The solution was left at room temperature for 3 h and then evaporated to give a residue which was recrystallized to give compound **19** (0.19 g; see Table I).

7-Cyano-3,3-dimethyl-1-(2-oxopyrrolidinyl)-3,4-dihydronaphthalene (27). 2-Pyrrolidinone (0.51 g, 6 mmol) in DMSO (5 mL) was added to a suspension of 80% NaH (0.18 g, 6 mmol) in DMSO (5 mL), and the mixture was stirred for 1 h at room temperature. A solution of epoxide **49** (1.0 g, 5 mmol) in DMSO (10 mL) was added dropwise, and the solution was stirred for 18 h. The mixture was cautiously diluted with H_2O and extracted with EtOAc. The extract was washed with H_2O and brine and dried. Filtration, evaporation, and chromatography on silica gel using EtOAc–pentane as eluent gave compound **27**, which was recrystallized (0.25 g) as pale yellow prisms (see Table I).

***trans*-4-Acetonyl-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol (16).** A solution of 1.7 M *n*-BuLi in hexane (29.6 mL, 0.05 mol) was added to a cooled solution of diisopropylamine (5.16 mL, 0.05 mol) in DME (25 mL) at such a rate as to keep the temperature at 0 °C. The reaction mixture was stirred for an additional 15 min, before addition of *tert*-butyl acetoacetate[12] (3.86 mL, 0.023 mol) during 10 min, at 0 °C. The reaction mixture was allowed to warm to room temperature, and epoxide **51** (1.0 g, 5 mmol) in DME (10 mL) was added to it. The reaction mixture was stirred for 20 h at room temperature and then cooled to 0 °C. HCl (32 mL of 10%) was added slowly to the orange mixture, followed by H_2O (20 mL), and the resulting solution was extracted with Et_2O. The organic phase was dried, filtered, and evaporated, and the residue was chromatographed on silica gel using a pentane–10% EtOAc in pentane gradient elution to give compound **52** (0.65 g, 37%) which was recrystallized from EtOAc–pentane: mp 121.5–122.5 °C. Anal. ($C_{20}H_{25}NO_5$) C, H, N.

To a solution of compound **52** (1.0 g, 2.8 mmol) in EtOH (50 mL) was added NaOH (0.28 g, 7 mmol) in H_2O (10 mL). The reaction was refluxed for 12 h and cooled, and H_2O (10 mL) was added. The solution was partially evaporated, acidified with dilute HCl, and extracted with EtOAc. The organic extract was washed with H_2O and brine and dried. Filtration and evaporation gave a gum that was radially chromatographed using a pentane–EtOAc gradient elution to give a gum that was recrystallized to give compound **16** (0.25 g; see Table I): NMR ($CDCl_3$) δ 1.20 [s, 3 H, $C(Me)_2$], 1.49 [s, 3 H, $C(Me)_2$], 2.32 (s, 3 H, COMe), 2.80–3.65 (m, 5 H, CH_2, H-4, H-3, and OH), 6.86 (d, 10, H-8), 7.30–7.50 (m, H-5 and H-7).

***trans*-6-Cyano-3,4-dihydro-*N*-methyl-2,2-dimethyl-2*H*-1-benzopyran-4-acetamide (21).** A 1.5 M solution of *n*-BuLi in hexane (6.5 mL, 10 mmol) was added dropwise to a solution of diisopropylamine (1.4 mL, 10 mmol) in dry THF (10 mL) at 0 °C, under N_2. A solution of *N*-methyl-*N*-(4-methoxybenzyl)-acetamide (1.93 g, 10 mmol) in THF (10 mL) was then added, and the solution was stirred for 0.5 h. A solution of epoxide **51** (2.0 g, 10 mmol) in THF (20 mL) was added to the mixture, which was allowed to attain room temperature and then refluxed for 2 h. The mixture was cooled and partitioned between EtOAc and H_2O. The organic layer was washed with dilute HCl, Na_2CO_3 solution, and brine and dried. Filtration and evaporation gave a gum which was triturated with 10% EtOAc–pentane to give a solid which was recrystallized from EtOAc–petroleum ether to give compound **53** (1.7 g; Scheme III) as a colorless solid with mp 156–157 °C. Anal. ($C_{23}H_{26}N_2O_4$) C, H, N.

A solution of compound **53** (0.5 g, 1.3 mmol) in $MeSO_3H$ (5 mL, 0.08 mol) was stirred at room temperature for 6 days. Water was added to the solution which was extracted with EtOAc. The organic extract was washed with $NaHCO_3$ solution and dried. Filtration, evaporation, and chromatography on silica gel using pentane-EtOAc in a gradient elution gave compound **21** (40 mg; see Table I).

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-4-[[(*N*,*N*-dimethylamino)carbonyl]methyl]-2*H*-1-benzopyran-3-ol (22).** A 1.5 M solution of *n*-BuLi in hexane (6.5 mL, 10 mmol) was added to a solution of diisopropylamine (1.4 mL, 10 mmol) in THF (10 mL) at 0 °C under N_2. A solution of *N*,*N*-dimethylacetamide (0.95 mL, 10 mmol) in THF (10 mL) was added to the solution which was stirred for 0.5 h. A solution of epoxide **51** (2.0 g, 10 mmol) in THF (20 mL) was added to the reaction mixture which was refluxed for 2 h. The mixture was cooled and partitioned between EtOAc and H_2O, and the organic layer was washed with dilute HCl, Na_2CO_3 solution, and brine and dried. Filtration, evaporation, and trituration with EtOAc–pentane gave a solid which was recrystallized to give compound **22** (0.7 g) as colorless plates (see Table I): NMR ($CDCl_3$) δ 1.20 [s, 3 H, $C(Me)_2$], 1.50 [s, 3 H, $C(Me)_2$], 2.70–3.70 (m, 4 H, CH_2, H-3 and OH overlapping), 3.05 (s, 3 H, NMe), 3.10 (s, 3 H, NMe), 5.20 (m, H-4), 6.85 (d, 8, H-8), 7.40 (m, H-5 and H-7).

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(*N*-methyl-2-oxo-3-pyrrolidinyl)-2*H*-1-benzopyran-3-ol (23).** A 1.5 M solution of *n*-BuLi in hexane (6.7 mL, 10 mmol) was added dropwise to a stirred solution of diisopropylamine (1.4 mL, 10 mmol) in THF (10 mL) at 0 °C, under N_2. A solution of *N*-methylpyrrolidone (0.96 mL, 10 mmol) in THF (20 mL) was added to the solution, followed after 0.5 h by a solution of epoxide **51** (2.0 g, 10 mmol) in THF (20 mL), and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled and partitioned between EtOAc and H_2O. The organic layer was washed with dilute HCl, Na_2CO_3 solution, and brine and dried. Filtration, evaporation, and recrystallization gave compound **23** (0.3 g; see Table I).

Pharmacological Testing. 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 B.P. recorder, Model No. 8005; each determination was the mean of at least six 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 had little or no effect on blood pressure apart from a slight reduction (by 5-10%) at 6 h postdose.

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Substrate Analogue Renin Inhibitors Containing Replacements of Histidine in P_2 or Isosteres of the Amide Bond between P_3 and P_2 Sites

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Incorporation of β-alanine or γ-aminobutyric acid in position P_2 of ACHPA or LeuΨ[CHOHCH$_2$]Val-based tetrapeptides gave highly active renin inhibitors (compounds V, VI, and XVII) with high specificity for renin and a remarkable stability against chymotrypsin. Replacement of the amide bond between P_2 and P_3 by isosteres (ketomethylenes, hydroxyethylenes, and the corresponding thio-insertion analogues) led to compounds (VIII-XIII, XVIII, and XIX) with renin inhibitory activity in the nanomolar range. Oral activity was achieved by incorporation of polar functionalities at the N-terminus of β-alanine-containing tetrapeptides. One of these compounds (XXVIII) was chosen for further studies. This inhibitor demonstrated excellent efficacy and a long duration of action after intravenous and oral administration to cynomolgus monkeys.

Introduction

The search for orally active renin inhibitors as therapeutic agents for the treatment of hypertension and congestive heart failure continues to represent a challenging target for medicinal chemists.[1] Analogues of the angiotensinogen region flanking the bond split by renin have turned out to be very potent and specific inhibitors of renin. However, the high affinity of these angiotensinogen analogues for human renin is often associated with fast hydrolysis between P_3 and P_2 sites[2] by the intestinal serine protease chymotrypsin.

Since stability against proteolytic attack in the digestive tract is a requirement for orally active peptides,[3] we focused our synthetic efforts on angiotensinogen analogues that are resistant to chymotrypsin and that retain a high specificity and high inhibitory potency for human renin.

Proteolytic stability has been achieved by incorporation of *N*-Me-histidine in P_2,[4] by alteration of the phenylalanine residue in P_3,[5] and by isosteric replacement of the amide bond connecting the P_3 and P_2 sites.[6] The latter approach led to inhibitors with moderate in vitro activity.

In this paper our results of replacing histidine in P_2 and of the isosteric substitution of the amide bond between P_3 and P_2 sites are described. We expected that resistance to proteolytic degradation in the digestive tract would lead to longer duration of action after intravenous and oral administration.

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