Relaxant Activity of 4-Amido-3,4-dihydro-2*H*-1-benzopyran-3-ols and 4-Amido-2*H*-1-benzopyrans on Guinea Pig Isolated Trachealis

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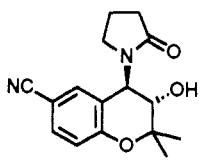
A series of 4-amido-3,4-dihydro-2*H*-1-benzopyran-3-ols and 4-amido-2*H*-1-benzopyrans related to the potassium channel activator cromakalim have been prepared and evaluated for their relaxant activity in guinea pig isolated tracheal spirals. Several analogues show enhanced relaxant activity relative to cromakalim in this preparation and the rank order of potency for those substituents investigated at C-6 was $CF_3 > CN > C_2H_5 >$ aza $\geq CH_3$. One compound, *trans*-3,4-dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-7-(trifluoromethyl)-2*H*-1-benzopyran-3-ol (**24**), was resolved into its two enantiomers and the activity was shown to reside essentially in the (+)-isomer, adding further support to the suggestion that the smooth muscle receptor for these potassium channel activators is stereoselective.

Introduction

Cromakalim (BRL 34915, **1**) is a member of a new class of pharmacologically active compounds, the potassium channel activators or openers, which have been extensively evaluated for their antihypertensive effects in animals.[1] A number of structurally distinct compounds have since been claimed which also relax vascular smooth muscle by a similar mechanism to that of cromakalim, but not all owe their antihypertensive action to this property alone.[2,3] Thus, while cromakalim,[2] pinacidil (**2**),[2] minoxidil sulfate (**3**),[3] and the recently identified compound RP49356 (**4**)[4] appear to exert their relaxant activity predominantly through the opening of potassium channels, others, such as nicorandil (**5**) and diazoxide (**6**), are less specific and can relax smooth muscle by other mechanisms in addition to the opening of potassium channels.[2,3]



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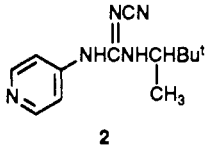

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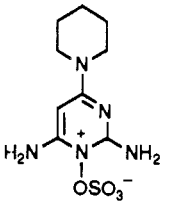

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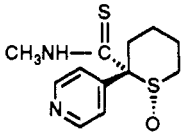

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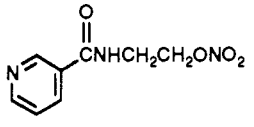

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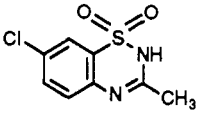

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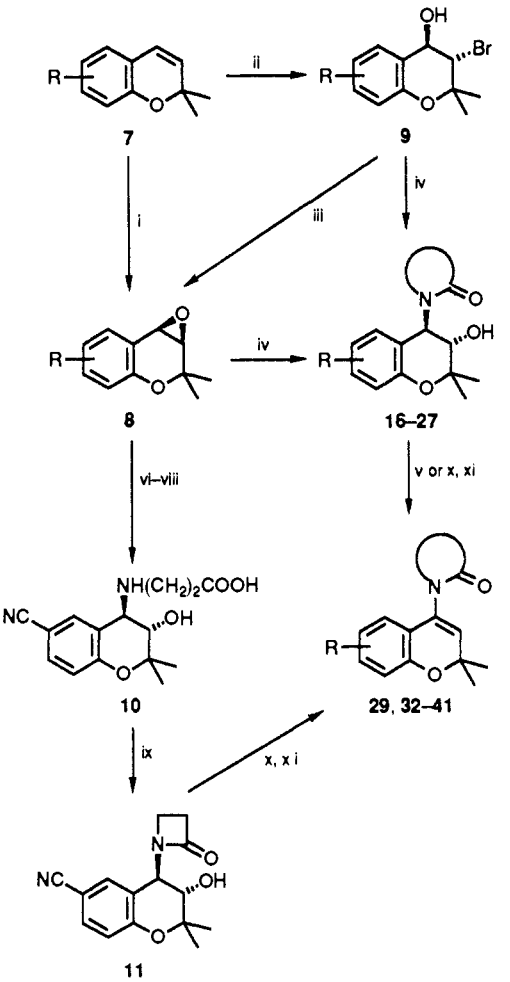
Although cromakalim has been shown to relax tissues other than vascular smooth muscle,[2] only relatively recently has it been shown to be an effective relaxant of airway smooth muscle in vivo.[5] These studies suggest that cromakalim may have potential as a bronchodilator in the treatment of asthma, and preliminary results in human volunteers[6] and asthmatics[7] support this contention. As a result of these studies, we have evaluated a series of analogues of cromakalim in an attempt to optimize bronchodilator activity.

Scheme I[a]



[a] Reagents: (i) mcpba, CH_2Cl_2; (ii) NBS, DMSO–H_2O; (iii) KOH, $(C_2H_5)_2O$; (iv) pyrrolidone or piperidone, KOBu^t, DMSO or excess lactam; (v) NaH, DMSO; (vi) NaN_3, aqueous dioxane; (vii) Zn, HCl, $(CH_3)_2CO$; (viii) propiolactone, DMF, 80 °C; (ix) Ph_3P, dipyridyl disulfide, CH_3CN, 50 °C; (x) CH_3SO_2Cl, $N(C_2H_5)_3$; CH_2Cl_2; (xi) KOBu^t, THF.

Chemistry

The most convenient routes to the target compounds

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(2) Hamilton, T. C.; Weston, A. H. *Gen. Pharmacol.* **1989**, *20*, 1. Edwards, G.; Weston, A. H. *Curr. Cardiovas. Pat.* **1989**, *1*, 1810.
(3) Bray, K. M.; Brown, B. S.; Duty, S.; Kay, P. B.; Longmore, J.; McHarg, A. D.; Newgreen, D. T.; Southerton, J. S.; Waterfall, J. F.; Weston, A. H. *Br. J. Pharmacol.* **1988**, *95*, 733P.
(4) Mondot, S.; Mestre, M.; Caillard, C. G.; Cavero, I. *Br. J. Pharmacol.* **1988**, *95*, 813P.
(5) Buckle, D. R.; Bumstead, J.; Clarke, G. D.; Taylor, J. F.; Taylor, S. G. *Br. J. Pharmacol.* **1987**, *92*, 744P. Arch, J. R. S.; Buckle, D. R.; Bumstead, J.; Clarke, G. D.; Taylor, J. F.; Taylor, S. G. *Br. J. Pharmacol.* **1988**, *95*, 763.
(6) Baird, A.; Hamilton, T. C.; Richards, D. R.; Tasker, T.; Williams, A. J. *Br. J. Clin. Pharmacol.* **1988**, *25*, 114P.
(7) Williams, A. J.; Vyce, T.; Richards, D. J.; Lee, T. *Allergy Proc.* **1988**, *9*, 249.

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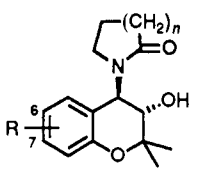
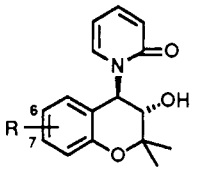
Table I. 4-Amido-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ols and 4-Amido-3,4-dihydro-2,2-dimethyl-2*H*-1-pyrano[3,2-*c*]pyridin-3-ols



11, 16, 17, 20–24



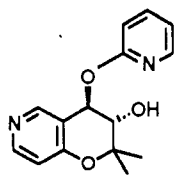
25–27

no.	R	*n*	% yield[a]	crystn solvent	mp, °C	formula	anal.
11	6-CN	0	16[b]	-	157–159	$C_{15}H_{16}N_2O_3$	M^+
16	6-CF_3	1	44	EtOAc–petroleum ether	181–182	$C_{16}H_{18}F_3NO_3$	M^+
17	6-CF_3	2	64	EtOAc	170–171	$C_{17}H_{20}F_3NO_3$	C,H,N
20	5-CF_3	2	83	EtOAc	137–138	$C_{17}H_{20}F_3NO_3$	C,H,N
21	7-CN	2	4[c]	-	176–178	$C_{17}H_{20}N_2O_3$	M^+
22	7-C_2H_5	2	76	-	130–131	$C_{18}H_{25}NO_3$	M^+
23	7-CF_3	1	87	EtOAc	166	$C_{16}H_{18}F_3NO_3$	H,N;C[d]
(±)-24	7-CF_3	2	74	EtOAc	163–164	$C_{17}H_{20}F_3NO_3$	C,H,N
(+)-24	7-CF_3	2		-	172–173	$C_{17}H_{20}F_3NO_3$	C,H,N
(-)-24	7-CF_3	2		-	170–171	$C_{17}H_{20}F_3NO_3$	C,H,N
25	6-CN	-	14	-	240–244[e]	$C_{17}H_{16}N_2O_3$	C,H,N
26	6-CF_3	-	24	-	178–182	$C_{17}H_{16}F_3NO_3$	C,H,N
27	6-aza	-	43[f]	-	206	$C_{15}H_{16}N_2O_3$	C,H,N

[a] From the epoxide direct method using 1 equiv of base except where otherwise noted. See the Experimental Section, method A. [b] Prepared by cyclization of the β-amino acid. [c] Via the epoxide formed in situ from the bromohydrin using 2–5 equiv of base. [d] C: calcd, 58.35; found, 57.91. [e] Literature mp 245–246 °C [Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492]. [f] Formed together with 3% of compound **28**, mp 180 ° dec.

start from the appropriately substituted benzopyran **7** following the previously established methods illustrated in Scheme I.[1] Typically, **7** was converted into the corresponding epoxide **8**, either directly with *m*-chloroperbenzoic acid or in situ from the bromohydrin **9** prepared by reaction with wet *N*-bromosuccinimide in DMSO. The method of choice is dependent to some extent on the nature of the aromatic substitution, although the direct synthesis was generally found to be more convenient. No attempt was made to optimize the procedure employed, and the epoxide, where isolated, was usually used without rigorous purification.

Rapid conversion of the isolated epoxides was found to be desirable in several instances, especially with the dihydropyranopyridine and 7-ethyl compounds, owing to their inherent instability. Reaction of either epoxide **7** or bromohydrin **9** at room temperature with lactam anions, generated with KOBu^t (or NaH for compound **25**) in DMSO or excess lactam as solvent, then afforded the corresponding 3,4-dihydrobenzopyranols **16**, **17**, **20–26** and dihydropyranopyridine **27** (Table I) in moderate to good yield in most instances. The occurrence of lower yields in some cases was attributable to incomplete reaction of epoxide **7** or to its concommitant hydrolysis to the 3,4-dihydroxy derivative. This was particularly evident with pyridone **25**, when some 27% of the 3,4-diol was isolated in addition to 18% unchanged epoxide. With the dihydropyranopyridine **27**, some 3% of the O-alkylated derivative **28** was also isolated, reflecting the ambident character of the 2-pyridone anion. The characterization of the pyridonyl compounds **25–27** as N-alkylated rather than as O-alkylated derivatives was evident from their ^{13}C NMR spectra, which showed chemical shifts for the pyridone moiety consistent with published data.[8]



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Attempts to prepare β-lactam **11** by direct methods were unsuccessful and it was therefore necessary to construct this compound in a different manner. Thus, epoxide opening with azide anion and reduction furnished the 4-amino-3,4-dihydrobenzopyranol which on condensation with propiolactone in DMF at 80 °C gave 54% of amino acid **10** (Scheme I). Reaction of **10** with triphenylphosphine and dipyridyl disulfide in acetonitrile at 50 °C then gave lactam **11**, albeit in relatively poor yield and of insufficient purity for elemental analysis (Table I).

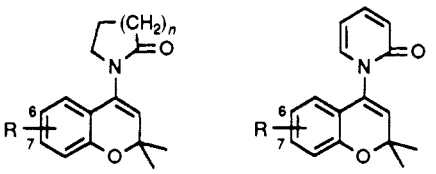
7-Trifluoromethyl compound **24** was resolved into its two enantiomers by reaction with (−)-α-methylbenzyl isocyanate in toluene at reflux followed by chromatographic separation of the two diastereoisomeric carbamates and subsequent regeneration of the alcohols with triethylamine and trichlorosilane.[1] ^1H NMR studies with cromakalim and its active 3*S*,4*R* enantiomer, BRL 38227, in $CDCl_3$ in the presence of the chiral solvent (*S*)-2,2,2-trifluoro-1-(9-anthryl)ethanol,[9] have demonstrated that both the C-2 methyl groups of BRL 38227 resonate downfield relative to the same signals of the 3*R*,4*S* enantiomer. Thus, for a solution containing a 2:1 ratio (3*S*,4*R*:3*R*,4*S*) of the above enantiomers in the presence of 2.84 equiv of chiral solvent, the axial and equatorial methyl groups of lemakalim resonate at 0.1 and 0.05 ppm, respectively, downfield of those in the 3*R*,4*S* enantiomer. In $CDCl_3$ alone, δ_{ax} = 1.28 ppm and δ_{eq} = 1.55 ppm.

Under the same experimental conditions, a similar relative shift was observed with the C-2 methyl groups of **24** and its active (+)-enantiomer. In this instance, the C-2Me_{ax} and C-2Me_{eq} signals resonate 0.05 and 0.025 ppm, respectively, downfield of the equivalent signals in the opposite enantiomer. These data are consistent with the assumption that the (+)-enantiomer of compound **24** has the same absolute configuration (3*S*,4*R*) as BRL 38227.

Dehydration of the amido alcohols of Table I was generally a facile process and in several instances substantial

(8) Barlin, G. B.; Brown, D. J.; Fenn, M. D. *Aust. J. Chem.* **1984**, *37*, 2391.
(9) Rinaldi, P. L. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 291.

Table II. 4-Amido-2,2-dimethylbenzopyrans and 4-Amido-2,2-dimethylpyrano[3,2-c]pyridines

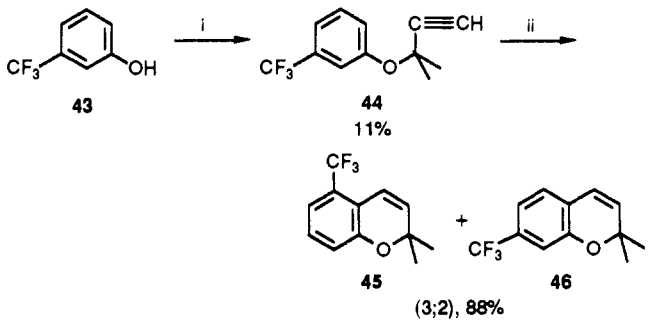


29, 32, 35–38 39–42

no.	R	n	% yield	mp, °C	formula	anal.	method[a]
29	6-CN	0	53	121–122	$C_{15}H_{14}N_2O_3$	M^+	C
32	6-CF_3	2	90	148	$C_{17}H_{18}F_3NO_2$	M^+	B
35	5-CF_3	2	38	125–126 sub	$C_{17}H_{18}F_3NO_2$	C,N;H[b]	B
36	7-CN	2	4[c]	182–186	$C_{17}H_{18}N_2O_2$	M^+	A
37	7-CF_3	1	93	80	$C_{16}H_{16}F_3NO_2$	C,H,N	B
38	7-CF_3	2	68	105–106 sub	$C_{17}H_{16}F_3NO_2$	C,H,N	C
39	6-CN	-	22[c]	149–151[d]	$C_{17}H_{14}N_2O_2$	C,H,N	A
40	6-CF_3	-	21[c]	126–129	$C_{17}H_{14}F_3NO_2$	C,H,N	A
41	6-aza	-	83	120–121	$C_{15}H_{14}N_2O_2$	C,H,N	B
42	6-aza *N*-oxide	-	98	>180 dec	$C_{15}H_{14}N_2O_3$	M^+	D

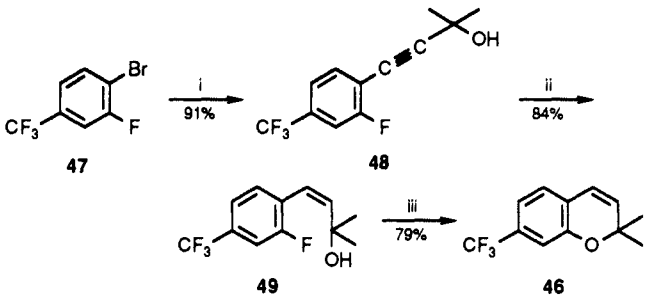
[a] See the Experimental Section. [b] H: calcd, 5.58; found, 6.18. [c] Formed together with the corresponding dihydrobenzopyranols. [d] Literature mp 144–146 °C [Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492].

Scheme II[a]



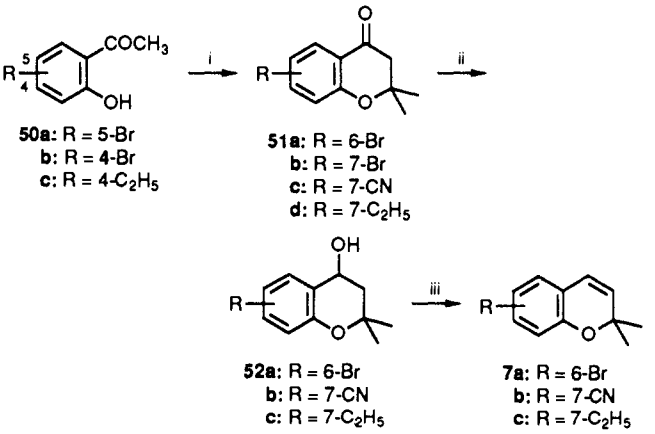
[a] Reagents: (i) $ClC(CH_3)_2C{\equiv}CH$, K_2CO_3, KI, $(CH_3)_2CO$; (ii) $PhN(C_2H_5)_2$, 160 °C.

Scheme III[a]



[a] Reagents: (i) $HC{\equiv}CC(CH_3)_2OH$, $(Ph_3P)_2PdCl_2$, CuI, $N(C_2H_5)_3$; Δ; (ii) $Pd/BaSO_4$, pyridine, H_2; (iii) NaH, DMSO, 60 °C.

Scheme IV[a]



[a] Reagents: (i) $(CH_3)_2CO$, pyrrolidine or piperidine, toluene, reflux; (ii) KBH_4, CH_3OH, 0 °C; (iii) ptsa, toluene, reflux.

amounts of the corresponding benzopyrans accompanied the amide coupling reactions. Thus, in the formation of pyridones **25** and **26**, significant quantities of **39** and **40**, respectively, were isolated (see Table II). As a rule, however, benzopyrans **29**, **32–40** and pyranopyridine **41** were prepared in reasonable yields by treatment of the corresponding amido alcohols with NaH in DMSO or THF at elevated temperatures (Table II). With β-lactam **11** and trifluoromethyl compound **24**, it was found preferable to generate the respective alkenes **29** and **38** by elimination of the corresponding mesylate with $KOBu^t$ in THF (Scheme I).

N-Oxide **42** was prepared from pyranopyridine **41** by reaction with *m*-chloroperbenzoic acid in chloroform.

Numerous methods are available for the synthesis of the precursor benzopyrans **7**, but for compounds derived from symmetrical phenols, that involving the Claisen rearrangement of appropriate propargyl ethers has been extensively used.[10] Moreover, the appreciable rate enhancement of the rearrangement and cyclization induced by the presence of *gem*-dimethyl groups on the carbon atom adjacent to the ether oxygen atom makes this procedure particularly suitable for the synthesis of the required compounds.[11] With *m*-substituted phenols, however, this method results in the formation of mixed C-5 and C-7 isomers,[12] making it less attractive for the preparation of C-7 substituted benzopyrans. This problem is illustrated for the trifluoromethyl analogue **46** (Scheme II), where the C-5 isomer **45** was preferentially formed. Furthermore, the two isomers were not chromatographically distinguishable at this stage, necessitating conversion to the corresponding epoxides prior to separation. To ov-

(10) Anderson, W. K.; LaVoie, E. J. *J. Org. Chem.* **1973**, *38*, 3832.
(11) Harfenist, M.; Thom, E. *J. Org. Chem.* **1972**, *37*, 841.
(12) Hepworth, J. D. In *Comprehensive Heterocyclic Chemistry*; Katritsky, A. R., Rees, C. W. Eds., 1984; Pergammon: Oxford, Vol. 3, p 737.

ercome the poor isolated yield of **46** formed in this reaction, an alternative synthesis (Scheme III) was developed in which halide **47** was regiospecifically coupled with 2-methylbut-3-yn-2-ol under Heck conditions[13] to generate acetylene **48** in excellent yield. Partial hydrogenation of **48** and base-induced cyclization then afforded a good overall yield of the requisite benzopyran **46**.

Unfortunately, the lack of appropriate starting materials precluded the use of this efficient method for other C-7 substituted benzopyrans. For this reason we have explored the unambiguous synthesis of such compounds from suitably substituted 2-hydroxyacetophenones **50** following the route shown in Scheme IV. Thus, reaction of **50a** with acetone and either pyrrolidine or piperidine in toluene following the procedure of Kabbe[14] furnished moderate yields of ketone **51a**, which was reduced to alcohol **52a** with potassium borohydride. Dehydration of **52a** with *p*-toluenesulfonic acid in toluene then gave 6-bromobenzopyran **7a**. 5-Bromophenol **50b** similarly gave ketone **51b** on treatment with acetone and piperidine, but in this instance the halogen atom was replaced by reaction with cuprous cyanide in DMF to give **51c** prior to reduction to **52b** and elimination to cyanobenzopyran **7b**. 7-Ethylbenzopyran **7c** was prepared from **50c** via the route described for **7a**, although in this case **52c** was formed together with the corresponding methyl ether and some **7c**. Treatment of this mixture with dilute hydrochloric acid, however, resulted in the formation of pure **7c**.

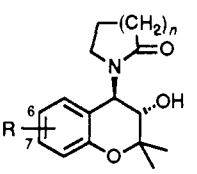
Results and Discussion

The antihypertensive activity of cromakalim is believed to be due to the opening of potassium channels in vascular smooth muscle.[15] As a consequence of this action, cromakalim facilitates the outward conductance of potassium ions down the electrochemical gradient with the result that the smooth muscle cell is hyperpolarized and rendered less sensitive to contractile (depolarizing) stimuli. This novel mechanism of action suggests that potassium channel activators may have potential in the treatment of other smooth muscle disorders, such as asthma, and our interest in cromakalim has therefore led to the evaluation of a number of analogues for their effects on isolated airway smooth muscle.

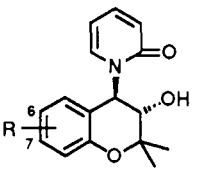
Compounds were routinely tested for their ability to relax spontaneously generated tone in guinea pig isolated tracheal spirals. Studies with cromakalim have shown it to relax tone induced in this tissue by a variety of different spasmogens,[16] but the relaxation of spontaneous tone distinguishes potassium channel activators from the calcium channel blockers such as nifedipine, which are only weakly effective. The β_2-adrenoceptor agonists, typified by salbutamol, are more potent relaxants of spontaneous tone in this preparation (Table III), but the maximum relaxation obtainable by these compounds and the potassium channel activators is similar. Aminophylline, by contrast, while causing relaxation, is of low potency.

Since earlier studies on the antihypertensive activity of amidodihydrobenzopyranols and amidobenzopyrans suggested that their potency as potassium channel activators diminished on replacement of the cyano function by hydrogen, halo, or (alkyloxy)carbonyl groups,[1] we restricted our studies to compounds without these substituents.

Table III. Inhibition of Spontaneous Tone in Guinea Pig Isolated Trachealis by 3,4-Dihydro-4-amido-benzopyran-3-ols and 3,4-Dihydro-4-amidopyrano[3,2-*c*]pyridin-3-ols



1, 11–24



25–27

no.[a]	R	*n*	IC_{50},[b] μM	IA[c]	*n*[d]
11	6-CN	0	>20		
1	6-CN	1	1.1 (0.6–1.9)	0.89 ± 0.02	7
12	6-CN	2	0.27 (0.13–0.58)	0.82 ± 0.04	4
13	6-CH_3	1	13.5 (3.23–57.1)	0.62 ± 0.16	4
14	6-CH_3	2	1.20 (0.55–2.62)	0.92 ± 0.02	6
15	6-C_2H_5	1	2.68 (1.05–6.8)	0.92 ± 0.03	4
16	6-CF_3	1	0.41 (0.17–0.99)	0.92 ± 0.00	4
17	6-CF_3	2	0.058 (0.055–0.061)	0.96 ± 0.02	4
18	6-aza	1	8.6 (2.3–32.0)	0.68 ± 0.09	4
19	6-aza	2	0.66 (0.51–0.84)	0.84 ± 0.06	4
20	5-CF_3	2	>20	0.13 ± 0.03	4
21	7-CN	2	>17	0.56	2
22	7-C_2H_5	2	2.25 (1.52–3.32)	0.83 ± 0.03	4
23	7-CF_3	1	0.73	0.90	2
(±)-24	7-CF_3	2	0.66 (0.49–0.89)	0.89 ± 0.02	15
(+)-24	7-CF_3	2	0.36 (0.14–0.99)	0.89 ± 0.02	4
(−)-24	7-CF_3	2	12.56 (7.28–21.67)	0.69 ± 0.05	4
25	6-CN	–	0.76 (0.45–1.25)	0.96 ± 0.02	4
26	6-CF_3	–	0.54	0.96	2
27	6-aza	–	5.1 (2.6–10.1)	0.81 ± 0.02	4
pinacidil			3.63 (1.93–6.82)	0.86 ± 0.04	10
nifedipine			>20	0.49 ± 0.05	10
salbutamol			0.018 (0.013–0.026)	0.98 ± 0.01	7
aminophylline			20.1 (17.3–29.2)	0.54 ± 0.08	7

[a] Compounds 1 and 12 prepared as in ref 1, and compounds 13–16, 18, and 19 as in ref 21. [b] IC_{50} with 95% confidence limits in parentheses. [c] Intrinsic activity ± SEM. [d] Number of determinations performed.

Nonetheless, where such compounds have been evaluated, their activity as relaxants of spontaneous tone in guinea pig trachealis parallels that in lowering blood pressure in spontaneously hypertensive rats.[17] Within the range of C-6 substituents studied, the rank order of potency as relaxants of guinea pig trachealis followed the sequence CF_3 > CN > C_2H_5 > aza ≥ CH_3 in both the dihydrobenzopyranol and, where comparisons are available, in the benzopyran series. The high potency found with the trifluoromethyl derivatives prompted a study of the positional effects of this substituent, where it was found that potency diminished in the order C-6 > C-7 > C-5 (dihydrobenzopyranols **17**, **24**, and **20** and benzopyrans **32**, **38**, and **35**, respectively). The influence of substitutional changes at C-7 in the limited number of examples studied was somewhat more complex. Particularly unusual was the poor activity seen in the cyanodihydrobenzopyranol **21** (Table III) compared to that of the cyanobenzopyran **36** (Table IV).

There was a general trend toward enhanced potency in the dihydrobenzopyranol δ-lactams (compounds **12**, **14**, **17**, and **19**) compared to the corresponding γ-lactams (compounds 1, **13**, **16**, and **18**, respectively) (Table III). This trend was less evident, however, in those benzopyrans where comparison is possible (cf. **30** and **31**, **33** and **34**, **37**, and **38**, Table IV). In the single example studied, contraction of the amide ring size to a β-lactam resulted in a further reduction in activity, although this was less pronounced in the benzopyrans (cf. **30** and **29**) than in the

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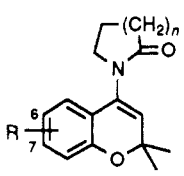
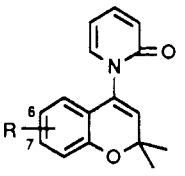
Table IV. Inhibition of Spontaneous Tone in Guinea Pig Isolated Trachealis by 4-Amidobenzopyrans and 4-Amidopyrano[3,2-c]pyridines



29–38



39–42

no.[a]	R	n	IC_{50},[b] μM	IA[c]	n[d]
29	6-CN	0	7.5	0.91	2
30	6-CN	1	1.57 (0.88–2.79)	0.91 ± 0.04	4
31	6-CN	2	1.1 (0.43–2.7)	0.90 ± 0.01	4
32	6-CF_3	2	0.65 (0.49–0.86)	0.89 ± 0.02	4
33	6-aza	1	6.7 (3.8–11.6)	0.67 ± 0.07	4
34	6-aza	2	2.2 (1.1–4.5)	0.92 ± 0.03	4
35	5-CF_3	2	>20	0.11	2
36	7-CN	2	3.96 (1.60–9.78)	0.86 ± 0.04	4
37	7-CF_3	1	5.1	0.97	2
38	7-CF_3	2	2.97 (2.41–3.65)	0.97 ± 0.01	10
39	6-CN		0.089 (0.052–0.150)	0.93 ± 0.02	5
40	6-CF_3		0.056 (0.049–0.064)	0.97 ± 0.01	4
41	6-aza		2.1 (0.8–5.1)	0.93 ± 0.03	4
42	6-aza, *N*-oxide		>20	0.01	4

[a] Compounds 30, 31 prepared as in ref 1, and 33 and 34 as in ref 21. [b] IC_{50} with 95% confidence limits in parentheses. [c] Intrinsic activity ± SEM. [d] Number of determinations.

corresponding dihydrobenzopyranols (cf. 1 and 11).

As a result of the potency of the δ-lactams, we studied the influence of replacing the C-4 piperidone ring of several derivatives by a 2-pyridone moiety. While the introduction of this unsaturation appeared to have no beneficial effect on potency in the dihydrobenzopyranols (cf. **12** and **25**, **17** and **26**, **19** and **27**), with the exception of the pyranopyridines (cf. **34** and **41**), it resulted in a significant increase in potency in the corresponding benzopyrans (cf. **31** and **39**, **32** and **40**). Unfortunately, however, this increase in potency with compounds **39** and **40** was not reflected in vivo on further evaluation in a guinea pig model of histamine-induced bronchoconstriction.[17] Subsequent to the completion of this work, other workers have reported on the antihypertensive activity of the 4-pyridonyl derivatives **25** and **39** and observed good in vivo activity in the rat.[18]

Since pinacidil (**2**) is known to be extensively metabolized in vivo to the weakly active *N*-oxide,[19] it was of interest to observe that *N*-oxide **42**, a potential metabolite of compound **41**, also had very poor in vitro potency (Table IV). The O-alkylated compound **28**, a byproduct in the formation of the precursor to **41**, was without activity at the concentrations tested (IC_{50} > 20 μM).

The vascular smooth muscle activity of the prototype compound cromakalim (**1**) has previously been shown to reside almost exclusively in the (−)-3*S*,4*R* enantiomer (BRL 38227), and we have shown that this extends to the action of the compound on airway smooth muscle.[5] Resolution of the trifluoromethyl compound **24** also demonstrated that the airway relaxant activity resided in a single isomer and NMR studies (reported above) suggest that this (+)-enantiomer also has the 3*S*,4*R* configuration. Similarly, the activity of pinacidil (**2**) has been shown to reside in the (−)-enantiomer,[20] suggesting that all these compounds act on a stereospecific receptor in smooth muscle to exert their relaxant effects. Further work on these and other specific potassium channel activators is needed, however, in order to aid the elucidation of the nature of this receptor.

Experimental Section

Melting points were determined with a Büchi melting point apparatus and are recorded uncorrected. The structures of all compounds were consistent with their IR and ^1H NMR spectra, which were determined with a Perkin-Elmer 298 spectrophotometer and a Varian EM390 90-MHz or JEOL GX270 70-MHz spectrometer, respectively. Mass spectra were recorded with a VG-micromass 70-70F spectrometer by using electron-impact techniques. Where represented by elemental symbols, the analyses of these elements fall within ±0.4% of the calculated values.

Substituted 2,2-Dimethyl-2*H*-1-benzopyrans. 3-Methyl-3-[3-(trifluoromethyl)phenoxy]but-1-yne (44). A mixture of 3-(trifluoromethyl)phenol (16.2 g, 0.1 mol), 3-chloro-3-methylbut-1-yne (12.0 g, 0.12 mol), anhydrous K_2CO_3 (16.8 g, 0.12 mol), and KI (1.5 g, 9 mmol) in dry acetone (100 mL) was stirred at reflux for 18 h and then cooled. After filtration of the inorganic material, the solvent was evaporated under vacuum and the resulting oil was chromatographed on silica gel (CH_2Cl_2–hexane 1:9) to give **44** (2.4 g, 11%) as a yellow oil which was used without further purification: IR ν_{max} (film) 3300, 1610, 1590, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (6 H, s, CH_3), 2.60 (1 H, s, C≡CH), 7.4 (4 H, m, aromatic).

2,2-Dimethyl-5- and -7-(trifluoromethyl)-2*H*-1-benzopyran (45 and 46). A solution of **44** (2.4 g, 10.5 mmol) in *N*,*N*-diethylaniline (12.5 mL) was heated at 160 °C under N_2 for 18 h, after which time the rearrangement was complete. The mixture was then cooled and added to 5 M HCl (1 L) and the product was extracted into ether. The organic phase was washed with brine, dried ($MgSO_4$), and evaporated to give a 3:2 mixture of **45** and **46**, respectively (2.1 g, 88%), as an oil which was used without further purification. Pure **46** was prepared by the unambiguous route illustrated below.

4-[2-Fluoro-4-(trifluoromethyl)phenyl]-2-methylbut-3-yn-2-ol (48). A mixture of 4-bromo-3-fluorobenzotrifluoride (8.45 g, 34.8 mmol), 2-methylbut-3-yn-2-ol (4.17 g, 43.5 mmol), bis(triphenylphosphine)palladium dichloride (1.22 g, 5 mol%) and CuI (0.67 g, 10 mol%) in NEt_3 (100 mL) was degassed and then heated to 110 °C under N_2 for 3 h. After cooling, the solution was filtered and evaporated under reduced pressure and the residual dark oil was dissolved in ether (400 mL). Treatment with charcoal, filtration, and evaporation then afforded crude **48** which was chromatographed on silica gel (CH_2Cl_2) to give pure material (7.78 g, 91%) as a colorless oil: IR ν_{max} (film) 3350 (br), 2240, 1625, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (6 H, s, CH_3), 3.65 (1 H, s, OH), 7.37 (3 H, m, aromatic).

(*Z*)-4-[2-Fluoro-4-(trifluoromethyl)phenyl]-2-methylbut-3-en-2-ol (49). A solution of **48** (7.78 g, 31.6 mmol) in pyridine (100 mL) was hydrogenated at atmospheric pressure over 5% $Pd/BaSO_4$ (1.0 g) until 1 equiv of H_2 was absorbed. The mixture was then filtered, diluted with ether (600 mL), and washed well with 2 M HCl. The ether phase was then dried ($MgSO_4$), evaporated under reduced pressure, and chromatographed on silica gel (CH_2Cl_2–hexane, 1:1) to yield **49** (6.61 g, 84%) as an oil: IR ν_{max} (film) 3400 (br), 1625, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (6 H, s, CH_3), 1.8 (1 H, s, OH), 5.83 (1 H, d, J = 12 Hz, C-3H), 6.26 (1 H, d, J = 12 Hz, C-4H), 7.33 (3 H, m, aromatic).

2,2-Dimethyl-7-(trifluoromethyl)-2*H*-1-benzopyran (46). Sodium hydride (0.038 g, 1.25 mmol of an 80% dispersion in mineral oil) and dry DMSO (2 mL) were stirred at 60 °C for 40 min and **49** (0.25 g, 1 mmol) in DMSO (0.5 mL) was added in one portion. After a further 1 h at 60 °C the mixture was cooled to ambient temperature and stirring was continued for an additional 12 h. Dilute HCl (2 M) was then added and the product was extracted into ether, the ethereal phase was dried ($MgSO_4$) and evaporated to dryness in vacuo. The residue was then chromatographed on silica gel (hexane) to afford **46** (0.18 g, 79%) as a

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colorless oil which was used without further purification: IR ν_{max} (film) 1640, 1620, 1575 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (6 H, s, CH_3), 5.83 (1 H, d, J = 10.5 Hz, C-3H), 6.47 (1 H, d, J = 10.5 Hz, C-4H), 7.20 (3 H, m, aromatic).

6-Bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one (51a). Pyrrolidine (13 mL, 1 equiv) was added to a solution of 2-hydroxy-5-bromoacetophenone (**50a**, 34.40 g, 0.16 mol, prepared by Fries rearrangement of the phenolic acetate) and acetone (68 mL, 5 equiv) in benzene (300 mL) and the mixture was heated under reflux for 16 h. After cooling, the solution was washed with 2 M HCl and the dried ($MgSO_4$) organic layer was evaporated to dryness. Chromatography on silica gel (hexane–EtOAc, 4:1) then afforded **51a** (24.48 g, 60%) which was used without further purification.

The 7-bromo and 7-ethyl derivatives (**51b** and **51d**, respectively) were prepared in ca. 60–80% yield by following the same procedure.

7-Cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-one (51c). Copper(I) cyanide (0.474 g, 5.34 mmol) was added to a solution of **51b** (1.1 g, 4.31 mmol) in DMF (20 mL) and the mixture was heated under reflux for 24 h. The cooled mixture was then poured into water, the organic material was extracted into ether, and the ethereal phase was dried ($MgSO_4$) and evaporated. The residual dark oil was chromatographed on silica gel ($CHCl_3$–hexane, 1:1) to give **51c** (0.53 g, 61%), which was suitable for further use without additional purification: ^1H NMR ($CDCl_3$) δ 1.5 (6 H, s, CH_3), 2.8 (2 H, s, C-3H), 7.3 (1 H, dd, J = 1.5, 8.5 Hz, C-6H), 7.32 (1 H, br s, C-8H), 8.05 (1 H, d, J = 8.5 Hz, C-5H).

7-Cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (52b). Potassium borohydride (0.142 g, 2.6 mmol) was added to a stirred suspension of **51c** (0.48 g, 2.4 mmol) in methanol (7 mL) at 0 °C and the mixture was maintained at this temperature for a further 30 min. After stirring for an additional 30 min at ambient temperature, 2 M HCl was added and the product was extracted into EtOAc. The extract was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was chromatographed on silica gel eluting with ether–hexane (2:1) to give essentially pure **52b** (0.39 g, 79%): ^1H NMR ($CDCl_3$) δ 1.3 (3 H, s, CH_3), 1.45 (3 H, s, CH_3), 2.0 (2 H, m, C-3H), 3.55 (1 H, m, OH), 4.85 (1 H, br dd, J = 6, 9 Hz, C-4H), 7.05 (1 H, d, J = 1 Hz, C-8H), 7.2 (1 H, dd, J = 1, 9 Hz, C-6H), 7.65 (1 H, d, J = 9 Hz, C-5H).

The corresponding 7-ethyl derivative **52c** and 6-bromo derivative **52a** were prepared in high yield following the same procedure, although in the case of **52c** the product was contaminated with some 4-methoxy compound and benzopyran **7c**.

7-Cyano-2,2-dimethyl-2*H*-1-benzopyran (7b). A mixture of **52b** (0.37 g, 1.82 mmol) and 4-toluenesulfonic acid (0.047 g, 0.248 mmol) in toluene (30 mL) was heated under N_2 at reflux for 4.5 h until dehydration was complete. The reaction was then cooled, filtered, and evaporated to furnish essentially pure **7b** (0.25 g, 73%): ^1H NMR ($CDCl_3$) δ 1.45 (6 H, s, CH_3), 5.8 (1 H, d, J = 10 Hz, C-3H), 6.4 (1 H, d, J = 10 Hz, C-4H), 7.0–7.3 (3 H, m, aromatic).

6-Bromo compound **7a** was prepared in a similar manner in 77% overall yield from dihydrobenzopyranone **51a**.

2,2-Dimethyl-7-ethyl-2*H*-1-benzopyran (7c). Dilute HCl (2 M, 100 mL) was added to a solution of crude **52c** (10.24 g, ca. 46.5 mmol) in dioxane (80 mL) and the mixture was stirred at ambient temperature for 4 days. Following extraction of the product into ether and concentration, **7c** (2.80 g, 30% from the benzopyranone **51d**) was isolated by chromatography on silica gel (hexane–CH_2Cl_2, 3:1): ^1H NMR ($CDCl_3$) δ 1.20 (3 H, t, J = 7.7 Hz, ethyl CH_3), 1.42 (6 H, s, CH_3), 2.56 (2 H, q, J = 7.7 Hz, ethyl CH_2), 5.53 (1 H, d, J = 9.6 Hz, C-3H), 6.29 (1 H, d, J = 9.6 Hz, C-4H), 6.64 (1 H, br s, C-8H), 6.66 (1 H, br d, J = 9 Hz, C-6H), 6.88 (1 H, d, J = 9 Hz, C-5H).

General Preparation of Bromohydrins 9. *trans*-3-Bromo-3,4-dihydro-2,2-dimethyl-7-(trifluoromethyl)-2*H*-1-benzopyran-4-ol (9, R = 7-CF_3). NBS (8.81 g, 49.6 mmol) was added to a cold (4 °C) solution of 2,2-dimethyl-7-(trifluoromethyl)-2*H*-1-benzopyran (**46**, 5.65 g, 24.8 mmol) in DMSO (50 mL) and water (0.89 mL). After the initial exothermic reaction had subsided, the solution was stirred at room temperature for 16 h and then poured into water. The product was extracted into EtOAc and the organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to afford the crude bromohydrin (8.0 g, 100%), which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.45 (3 H, s, CH_3), 1.68 (3 H, s, CH_3), 3.33 (1 H, d, J = 5 Hz, OH), 4.12 (1 H, d, J = 8 Hz, C-3H), 4.9 (1 H, dd, J = 5, 8 Hz, C-4H), 7.12 (1 H, br s, C-8H), 7.23 (1 H, br d, J = 8 Hz, C-6H), 7.62 (1 H, d, J = 8 Hz, C-7H).

General Preparation of Epoxides 8. (a) Direct: 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyrans (8). To a stirred solution of benzopyran (**7**, 10 mmol) in CH_2Cl_2 (35 mL) was added *m*-chloroperbenzoic acid (2.15 g, 10 mmol of 80% pure material) and the mixture was stirred at ambient temperature for 24 h. The precipitate was filtered off and the filtrate was washed with aqueous Na_2SO_3 followed by aqueous $NaHCO_3$. The dried ($MgSO_4$) organic phase was evaporated in vacuo to give crude epoxide **8**. Chromatography on silica gel ($CHCl_3$–hexane, 3:7) then afforded ~80% of material of sufficient purity for subsequent reaction.

(b) Indirect: 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-6-(trifluoromethyl)-2*H*-1-benzopyran (8, R = 6-CF_3). A mixture of *trans*-3-bromo-3,4-dihydro-2,2-dimethyl-6-(trifluoromethyl)-2*H*-1-benzopyran-4-ol (4.0 g, 12 mmol) and KOH pellets (4.0 g, 71 mmol) in dry ether (500 mL) was stirred vigorously for 48 h and the inorganic material was then removed by filtration. Evaporation of the solvent under reduced pressure then gave the required epoxide (2.5 g, 83%), which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s, CH_3), 1.60 (3 H, s, CH_3), 3.45 (1 H, d, J = 4 Hz, C-3H), 3.85 (1 H, d, J = 4 Hz, C-4H), 6.80 (1 H, d, J = 8 Hz, C-8H), 7.50 (2 H, m, C-5H and C-7H).

General Preparation of 3,4-Dihydrobenzopyran-3-ols of Table I. Method A. *trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-7-(trifluoromethyl)-2*H*-1-benzopyran-3-ol (24). 2-Piperidone (108 mg, 1.1 mmol) and $KOBu^t$ (130 mg, 1.15 mmol) were stirred in DMSO (3 mL) under N_2 for 30 min and 3,4-dihydro-2,2-dimethyl-3,4-epoxy-7-(trifluoromethyl)-2*H*-1-benzopyran (120 mg, 0.49 mmol) was added. The mixture was stirred overnight followed by an aqueous workup and chromatography on silica gel (CH_2Cl_2–hexane, 1:1). Recrystallization from EtOAc then gave **24** (125 mg, 74%): mp 163–164 °C; IR ν_{max} (mull) 3250, 2920, 1620, 1600, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 1.75 (4 H, m, C-4′ and C-5′H), 2.60 (2 H, t, J = 7 Hz, C-3′H), 2.94 (1 H, m, C-6′H), 3.06 (1 H, m, C-6′H), 3.3 (1 H, d, J = 5 Hz, OH), 3.81 (1 H, dd, J = 5, 10 Hz, C-3H), 5.95 (1 H, d, J = 10 Hz, C-4H), 7.1 (3 H, m, aromatic). Anal. ($C_{17}H_{20}F_3NO_3$) C, H, N.

Resolution of *trans*-3,4-Dihydro-2,2-dimethyl-4-(2-oxopiperidin-1-yl)-7-(trifluoromethyl)-2*H*-1-benzopyran-3-ol (24). A solution of racemic **24** (730 mg, 2.13 mmol) and (−)-α-methylbenzyl isocyanate (0.35 mL, 2.47 mmol) in dry toluene (20 mL) was heated at reflux for 39 h to complete formation of the diastereoisomeric carbamates and the cooled mixture was evaporated to dryness. Chromatography of the residue on silica gel ($CHCl_3$–hexane, 9:1) then gave the carbamate of (−)-**24** (270 mg, 26%) and of (+)-**24** (255 mg, 24%) together with 360 mg (35%) of unseparated isomers. Hydrolysis of each carbamate in turn by treatment with NEt_3 (2 equiv) and trichlorosilane (2 equiv) at 35 °C for 18 h afforded the pure enantiomers of **24**.

The (−)-enantiomer (132 mg, 70%): mp 170–171 °C; $[\alpha]_D$ −11.9° (c = 0.17, $CHCl_3$). Anal. ($C_{17}H_{20}F_3NO_3$) C, H, N. The (+)-enantiomer (125 mg, 70%): mp 172–173 °C; $[\alpha]_D$ +12.1° (c = 0.16, $CHCl_3$). Anal. ($C_{17}H_{20}F_3NO_3$) C, H, N.

***trans*-4-Azido-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol.** Sodium azide (390 mg, 6 mmol) was added to a stirred solution of **8** (R = 6-CN, 1.05 g, 5.22 mmol)[1] in dioxane (10.5 mL) and water (2.1 mL), and the resulting red solution was stirred at room temperature for 91 h. After heating of the solution under reflux (2.5 h), it was cooled and diluted with water, and the organic material was extracted into ether. The dried ethereal phase ($MgSO_4$) was evaporated to yield the title compound (1.20 g, 94%): mp (light petroleum–ether) 137 °C; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 2.73 (1 H, d, J = 6 Hz, OH), 3.8 (1 H, dd, J = 6, 9 Hz, C-3H), 4.47 (1 H, d, J = 9 Hz, C-4H), 6.90 (1 H, d, J = 8 Hz, C-8H), 7.53 (1 H, dd, J = 2, 8 Hz, C-7H), 7.77 (1 H, d, J = 2 Hz, C-5H). Anal. ($C_{12}H_{12}N_4O_2$) C, H, N.

***trans*-4-Amino-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol.** To a stirred solution of the above azide (144

mg, 0.59 mmol) in acetone (2.4 mL) containing concentrated HCl (0.445 mL) was added Zn dust (0.445 g, 6.81 mmol) portionwise. After 2 h the inorganic material was filtered from the solution and the filtrate was diluted with water and made alkaline with 2 M NaOH. The product was extracted into ether, and the dried extracts ($MgSO_4$) were evaporated and chromatographed on silica gel ($CHCl_3$) to afford the amino alcohol (97 mg, 75%) which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.24 (3 H, s, CH_3), 1.53 (3 H, s, CH_3), 2.80 (3 H, m, OH, NH_2), 3.38 (1 H, d, J = 7 Hz, C-4H), 3.73 (1 H, br d, J = 7 Hz, C-3H), 6.87 (1 H, d, J = 6 Hz, C-8H), 7.46 (1 H, dd, J = 1, 6 Hz, C-7H), 7.8 (1 H, d, J = 1 Hz, C-5H).

***trans*-4-[(2-Carboxyethyl)amino]-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol (10).** A solution of *trans*-4-amino-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol (1.21 g, 5.55 mmol) and β-propiolactone (0.35 mL, 5.56 mmol) in DMF (25 mL) was heated at 80 °C for 2 days and the reaction mixture was cooled and concentrated in vacuo. Chromatography on silica gel, with gradient elution from EtOAc–MeOH (99:1) to MeOH, gave **10** (0.86 g, 54%) as a yellow foam which was used without further purification: ^1H NMR ($CDCl_3$) δ 1.20 (3 H, s, CH_3), 1.50 (3 H, s, CH_3), 2.6 (3 H, m, C-2'H, OH), 2.9 (1 H, m, C-1'H), 3.1 (1 H, m, C-1'H), 3.9 (1 H, d, J = 9.5 Hz, C-3H), 4.4 (1 H, m, C-4H), 6.9 (1 H, d, J = 8.5 Hz, C-8H), 7.45 (1 H, br d, J = 8.5 Hz, C-7H), 7.55 (2 H, br, NH, CO_2H), 8.05 (1 H, br s, C-5H).

***trans*-6-Cyano-3,4-dihydro-2,2-dimethyl-4-(2-oxoazetidin-1-yl)-2*H*-1-benzopyran-3-ol (11).** To a solution of triphenylphosphine (0.34 g, 1.25 mmol) and 2-dipyridyl disulfide (0.27 g, 1.25 mmol) in acetonitrile (50 mL) was added **10** (0.301 g, 1.04 mmol) and the mixture was heated at 50 °C for 18 h. After cooling, the solution was evaporated to dryness and the residual yellow oil was chromatographed on silica gel ($CHCl_3$–Et_2O, 1:1) to elute triphenylphosphine oxide and 2-mercaptopyridine. Further elution (EtOAc–MeOH, 9:1) gave crude **11** (0.16 g) which was purified by preparative thin-layer chromatography (Et_2O–$CHCl_3$–MeOH, 73:25:2) to give **11** (0.05 g, 16%) as a white solid: mp 157–159 °C; ^1H NMR ($CDCl_3$) δ 1.25 (3 H, s, CH_3), 1.55 (3 H, s, CH_3), 3.15 (3 H, m, C-3'H, C-4'H), 3.35 (1 H, m, C-4'H), 3.75 (1 H, d, J = 9.9 Hz, C-3H), 4.5 (1 H, br, OH), 4.9 (1 H, d, J = 9.9 Hz, C-4H), 6.9 (1 H, d, J = 8.5 Hz, C-8H), 7.45 (2 H, m, C-5H, C-7H); MS found M^+ 272.1160 ($C_{11}H_{16}N_2O_3$ requires 272.1161).

General Preparation of Benzopyrans of Table II. Method B. 2,2-Dimethyl-4-(2-oxopyrrolidin-1-yl)-7-(trifluoromethyl)-2*H*-1-benzopyran (37). A mixture of the benzopyranol (**23**, 0.19 g, 0.61 mmol) and NaH (18.5 mg, 0.61 mmol of an 80% dispersion in mineral oil) was dissolved in dry THF (10 mL) and then heated to reflux for 15 h. The solvent was evaporated and the residue was partitioned between water and EtOAc. The organic phase was separated, washed with water and brine, dried ($MgSO_4$), and evaporated under reduced pressure. The product was then chromatographed on silica gel ($CHCl_3$) to afford **37** (0.85 g, 48%). Recrystallization (EtOAc–hexane) furnished material of mp 80 °C; ^1H NMR ($CDCl_3$) δ 1.50 (6 H, s, CH_3), 2.20 (2 H, m, C-4'H), 2.57 (2 H, t, J = 7.5 Hz, C-3'H), 3.62 (2 H, t, J = 7.5 Hz, C-5'H), 5.72 (1 H, s, C-3H), 7.0–7.1 (3 H, m, aromatic). Anal. ($C_{16}H_{16}F_3NO_2$) C, H, N.

Method C. 2,2-Dimethyl-4-(2-oxopiperidin-1-yl)-7-(trifluoromethyl)-2*H*-1-benzopyran (38). A mixture of the benzopyranol (**24**, 1.47 g, 4.28 mmol), NEt_3 (3.6 mL, 25.8 mmol), and methanesulfonyl chloride (1.99 mL, 25.8 mmol) in CH_2Cl_2 (60 mL) was stirred at ambient temperature for 20 h and then washed with 2 M HCl, saturated $NaHCO_3$, and brine. The dried ($MgSO_4$) solution was evaporated in vacuo, the residue dissolved in THF (70 mL), and KO^{t}Bu (1.02 g, 8.56 mmol) was added. The resulting solution was stirred at room temperature for 4 h and then concentrated to dryness. The residue was then redissolved in CH_2Cl_2, washed with brine, dried ($MgSO_4$), and evaporated. Chromatography of the resulting gum on silica gel ($CHCl_3$–Et_2O, 1:1) and sublimation at 105 °C (0.1 mmHg) then gave **38** (0.95 g, 68%): mp 105–106.5 °C; ^1H NMR ($CDCl_3$) δ 1.49 (3 H, s, CH_3), 1.52 (3 H, s, CH_3), 1.94 (4 H, m, C-4'H and C-5'H), 2.55 (2 H, m, C-3'H), 3.46 (2 H, m, C-6'H), 5.67 (1 H, s, C-3H), 6.95 (1 H, d, J = 8 Hz, C-5H), 7.8 (2 H, m, C-6H and C-8H). Anal. ($C_{17}H_{18}F_3NO_2$) C, H, N.

Method D. 2,2-Dimethyl-4-(2-pyridon-1-yl)-2*H*-pyrano[3,2-*c*]pyridine *N*-Oxide (42). *m*-Chloroperbenzoic acid (0.32 g, 1 equiv of 85% pure material) was added to a solution of **41** (0.254 g, 1 mmol) in $CHCl_3$ (4 mL) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel ($CHCl_3$–CH_3OH, 19:1) to give **42** (0.265 g, 98%); mp >180 °C dec; IR ν_{max} (mull) 2985, 1665, 1590, 1440, 1265, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (3 H, s, CH_3), 1.66 (3 H, s, CH_3), 5.96 (1 H, s, C-3H), 6.33 (1 H, dt, J_t = 7.5 Hz, J_d = 1.5 Hz, C-5'H), 6.65 (1 H, d, J = 9 Hz, C-3'H), 6.84 (1 H, d, J = 7.5 Hz, C-8H), 7.25 (1 H, dd, J = 1.5, 7 Hz, C-6'H), 7.4–7.6 (1 H, m, C-4'H), 7.70 (1 H, s, C-5), 8.05 (1 H, d, J = 7 Hz, C-7H). MS found M^+ 270.0989 ($C_{15}H_{14}N_2O_3$ requires 270.1005).

Relaxation of Guinea Pig Isolated Tracheal Spirals. Guinea-pig tracheal spiral strips were prepared and suspended under isometric conditions in oxygenated Krebs solution. Tension was allowed to develop spontaneously and was maintained at 2 g. Compounds were added in a cumulative fashion and the inhibitory effects were calculated as a percentage of the relaxation induced by isoprenaline (10^{-3} M) added at the end of the experiment. The IC_{50} value of each compound was that concentration which produced 50% of the response to isoprenaline, as measured from the dose–response curve, and was generally a geometric mean of four or more determinations. The intrinsic activity (IA) for each compound was calculated as the ratio of its maximum relaxant activity over that produced by isoprenaline and expressed as an arithmetic mean.

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