2,2-Dialkylnaphthalen-1-ones as New Potassium Channel Activators

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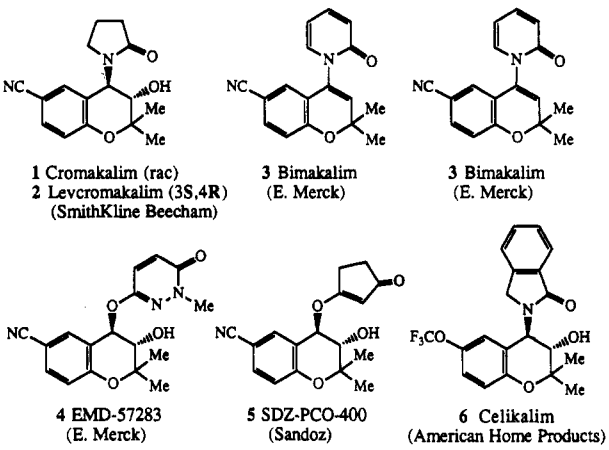
A new series of 2,2-dialkylnaphthalen-1-one potassium channel activators has been prepared, and their *in vitro* relaxant activities in isolated rat portal vein and guinea pig tracheal spirals as well as their oral antihypertensive effect in spontaneously hypertensive rats have been evaluated. The group of 1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethylnaphthalen-1-ones with an electron-withdrawing substituent at the 6-position contain the most active compounds and 1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carbonitrile, **17f** (UR-8225), has been selected for further pharmacological development.

Potassium channels are diverse and widely distributed in a variety of tissues, and their modulators are of considerable pharmacological importance.[1] Potassium channel blockers have been used for many years as oral hypoglycaemic agents and may have potential as antiarrythmic agents and appetite suppressants.[2] Recent years have also seen increased interest in the development of compounds that open potassium channels. This process is related to the relaxation of a number of smooth muscle types, through a mechanism[3] that roughly implies loss of potassium from the cell and subsequent hyperpolarization of membrane potential. As a result, the intracellular calcium concentration falls, producing the cell relaxation. Potassium channel activators are thus promising in cardiovascular therapy as antihypertensives and coronary vasodilators. They may also be useful as cardioprotective agents and in the treatment of diseases such as asthma, urinary incontinence, and irritable bladder syndrome, provided that good levels of selectivity can be achieved.

There are several structural groups in this class of compounds[4] represented by Nicorandil, Pinacidil, Minoxidil sulphate, Diazoxide, Aprikalim (RP-52891), and Cromakalim, **1**, this last a potent antihypertensive agent and the first benzopyran potassium channel activator to enter clinical trials. The product was recently substituted for development by its active enantiomer Levcromakalim, **2**, which is now in phase II and III clinical trials as a long-term antihypertensive.[5] The substituents at different positions of the benzopyran ring have been modified in a number of structure/activity studies,[6] and currently several compounds are being developed by pharmaceutical companies[5] (Chart I shows some). The benzopyran nucleus itself has also been modified, and series of thiobenzopyranes,[7] pyranopyridines,[8] thienopyrans,[9] tetrahydroquinolines and tetrahydronaphthalenes,[10] benzoxepines,[11] 1,4-benzoxazines,[12] 1,3-benzoxazines,[13] and indans[14] have been prepared.

This paper describes a structure/activity study on a new modification of the benzopyran ring, in which the benzopyran oxygen has been substituted by a carbonyl group[15] giving rise to a new potent series of potassium channel openers. Although structurally different from previously reported potassium channel openers, the 1-naphthalenones here described act by opening ATP-sensitive potassium channels. Representative compounds inhibited the rat aorta contractions induced by 30 mM KCl but not those induced by 80 mM KCl, and their effects in isolated rat aortae and portal veins were competitively inhibited by glibenclamide.[15c,d]

Chart I[a]



[a] Potassium channel openers under development.

Chemistry

The synthesis of the present compounds involves opening the new 3,4-epoxy derivatives **12**, which are obtained following the route outlined in Scheme I. The requisite 1-tetralones **9** are either commercially available (R = H, 6-OMe) or can be obtained using published procedures.[16]

Alkylation of **9** (NaH, MeI, C_6H_6) afforded good yields of the dimethyl derivatives **10** (Table I). Where R = 6-NHAc, a simultaneous methylation of the amide group occurred. The 6-Br derivative **10e** was converted at this stage to the phenyl sulfide and perfluoroalkyl derivatives **10h**, **10k**, and **10l** as shown in Scheme II.

Bromination of compounds **10** with NBS/$(PhCO)_2O_2$/CCl_4 followed by immediate basic elimination gave olefins **11** (Table I). For nonhydrolizable substituents at position 6, KOH in EtOH was used as the eliminating agent, whereas for groups susceptible to nucleophile attack, DBU proved to be the reagent of choice. Variable amounts of 4-bromo olefins were also detected at the end of the process. Their presence, which presumably arises from a 4,4-dibromo intermediate, was minimized by careful control of the reaction time.

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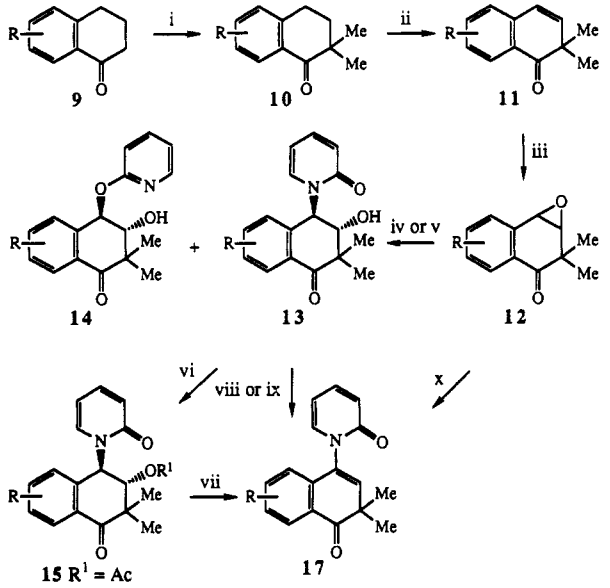
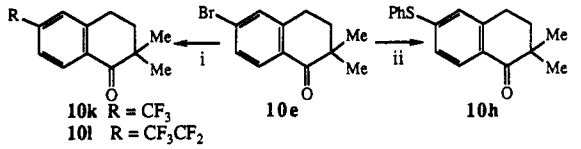
Scheme I[a]



a: R = H; b: R = 6-OMe; c: R = 6-F; d: R = 6-Cl; e: R = 6-Br; f: R = 6-CN; g: R = 6-NHAc; h: R = 6-SPh; i: R = 6-SO_2Ph; j: R = 6-NMeAc; k: R = 6-CF_3; l: R = 6-CF_2CF_3; m: R = 6,7-Cl_2; n: R = 7-Br; o: R = 7-CN

[a] (i) NaH, IMe, PhH, reflux; (ii) (1) NBS, CCl_4, 60 °C; (2) KOH, EtOH, 45 °C or DBU, 85 °C; (iii) MCPBA, CH_2Cl_2; (iv) method A: 2-pyridone, pyridine, EtOH, reflux; (v) Method B: 2-[(trimethylsilyl)oxy]pyridine, $FNBu_4$, THF; (vi) Ac_2O (or HCHO), pyridine; (vii) method C: DBU, PhMe, reflux; (viii) method D: NaOH–SiO_2, dioxane, reflux; (ix) For R = CN: CuCN, NMP, reflux; (x) method E: 2-[(trimethylsilyl)oxy]pyridine, $FNBu_4$, THF, reflux.

Scheme II[a]



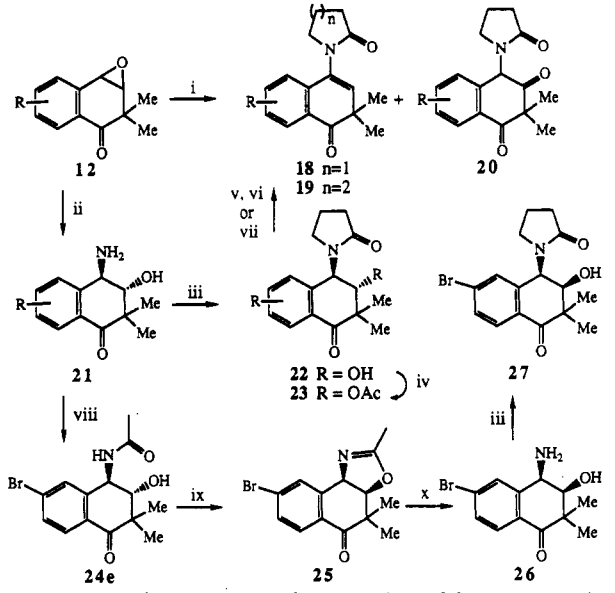
[a] (i) CF_3CO_2Na (or $CF_3CF_2CO_2Na$), CuI, NMP, reflux; (ii) PhSH, K_2CO_3, NMP, 160 °C.

In all cases treatment of olefins **11** with MCPBA/CH_2Cl_2 afforded good yields of the epoxides **12** (Table I), while the alternative route via bromohydrin formation and subsequent elimination with base could not be applied as olefins **11** failed to react with NBS. Epoxidation of **11h** (R = 6-PhS) yielded the sulfonyl derivative **12i** as expected.

The opening of the key epoxides **12** with 2-pyridone was performed either directly using the reagent in refluxing ethanol[17] (method A) or via its *O*-silyl derivative[18] (method B) to afford good yields of the *trans*-alcohols **13** (Table II). Minor amounts of adducts **14** (Table IV), resulting by oxygen attack, were also formed in both cases, but they were easily separated from **13** by silica chromatography. Acetylation and formylation of compounds **13** afforded **15** and **16**, respectively.

The elimination products **17** (Table II) were obtained by heating the 3-acetyl derivatives **15** with DBU in refluxing toluene[19] (method C), from the 3-hydroxy derivatives **13** (NaOH, SiO_2, dioxane)[17] (method D), or directly from epoxides **12** employing 2-TMSO-pyridine in refluxing THF (method E). Reaction of the 6-Br derivatives **13e** and **13n** with CuCN in NMP[20] underwent both cyano exchange and elimination to afford compounds **17f** and **17o**.

Scheme III[a]



[a] (i) 2-Pyrrolidone or 2-piperidone, NaH, DMSO; (ii) NH_3,EtOH, reflux; (iii) (1) $ClCO(CH_2)_3Cl$, NEt_3, $CHCl_3$; (2) K_2CO_3, KI, acetone, reflux; (iv) Ac_2O, pyridine; (v) DBU, PhMe, reflux; (vi) NaOH–SiO_2, dioxane, reflux; (vii) CuCN, NMP, reflux; (viii) $ClCOCH_3$, NEt_3, $CHCl_3$; (ix) DAST, CH_2Cl_2; (x) 6 N HCl, reflux.

Other R substituents were introduced in the last step of the synthesis. Thus, treatment of the 6-bromo derivative **17e** with TMSC≡CH (PPh_3, $PdAc_2$, TEA)[21] afforded **17p**, which was transformed to the 6-ethynyl derivative **17q** upon deprotection with K_2CO_3. This, in turn, was partially hydrogenated to the 6-ethenyl derivative **17s** (H_2, Lindlar cat., quinoline, EtOH) or completely reduced to the 6-ethyl compound **17r** (H_2, 5% Pd/C, EtOAc). Use of EtOH as the solvent in this latter step proved detrimental as olefin and pyridone hydrogenation was also observed. Acetyl derivative **17t** was prepared in one step from the ethynyl derivative **17q** upon reaction with $Hg(OAc)_2$. The 6-cyano derivative **17f** served as the starting point for the synthesis of the carboxylic acid derivatives. Thus, using standard chemical transformations, the imidate **17u** (MeONa, MeOH), the acid **17v** (6 N HCl), the methyl ester **17w** (MeOH, HClg), or the amide **17j** (KOH, ^{t}BuOH) was prepared. Finally, the 6-MeNH derivative **17y** was prepared by acid hydrolysis of its acetamide (6 N HCl).

The opening of epoxides **12** with 2-pyrrolidone or 2-piperidone (NaH, DMSO)[22] directly afforded a mixture of the unsaturated compounds (**18** and **19**, respectively) and diketones **20** in poor yields (Scheme III). The 3-hydroxy-4-pyrrolidones **22** were obtained following an alternative route involving the opening of epoxides **12** with ammonia in EtOH, acylation with 4-chlorobutyryl chloride, and cyclization to the pyrrolidone ring (K_2CO_3, KI, acetone).[22] In a similar way to that described for the 4-pyridone derivatives, alcohol **22** afforded the 3-acetoxy **23** and the unsaturated compounds **18**.

The *cis*-amino alcohol **26** was obtained by acidic hydrolysis of the somewhat unstable oxazoline **25**, which was prepared from amine **21e** by acetylation followed by cyclization with DAST.[23] The *cis*-3-hydroxy-4-pyrrolidone **27** was obtained from **26** in a manner similar to that described for the *trans* derivative **22**.

The acyclic amides **24f** and **28–36** (Table III) were obtained by acylation of amine **21f** either with acetyl chloride in chloroform (**24f**) or with the corresponding carboxylic acids and DCC in DMF (**28–36**). Compound

Table I. New Tetrahydronaphthalen-1-ones **10**, Dihydronaphthalen-1-ones **11**, Epoxides **12**, and Amino Alcohols **21**

compd	R	yield, %	mp, °C bp, °C (mmHg)	recryst solvent	formula	anal.[a]
10b	6-OMe	100	118–120 (0.5)		$C_{13}H_{16}O_2$	C,H[b]
10c	6-F	70	130–135 (0.5)		$C_{12}H_{13}FO$	C,H
10d	6-Cl	84	155–160 (0.6)		$C_{12}H_{13}ClO$	C,H
10e	6-Br	80	155–160 (0.5)		$C_{12}H_{13}BrO$	C,H
10f	6-CN	73	142–144	CH_2Cl_2	$C_{13}H_{13}NO$	C,H,N
10h	6-SPh	81	220–225 (0.5)		$C_{18}H_{18}SO$	C,H
10j	6-NMeAc	77	92–94	EtOAc	$C_{15}H_{19}NO_2 \cdot 0.1H_2O$	C,H,N
10k	6-CF_3	59	28–30		$C_{13}H_{13}F_3O$	C,H
10l	6-CF_2CF_3	63	130–135 (0.9)		$C_{14}H_{13}F_5O$	C,H
10m	6,7-Cl_2	90	64–68	Et_2O	$C_{12}H_{12}Cl_2O$	C,H
10n	7-Br	90	145–150 (0.5)		$C_{12}H_{13}BrO$	C,H
11b	6-OMe	40	120–130 (0.5)		$C_{13}H_{14}O_2$	C,H
11c	6-F	100	30–40 (0.5)		$C_{12}H_{11}FO$	C,H
11d	6-Cl	93	150–160 (0.6)		$C_{12}H_{11}ClO \cdot 0.75H_2O$	C,H
11e	6-Br	74	49–52		$C_{12}H_{11}BrO$	C,H
11f	6-CN	68	104–105	CH_2Cl_2	$C_{13}H_{11}NO$	C,H,N
11h	6-SPh	90	215–220 (0.5)		$C_{18}H_{16}OS \cdot 0.25H_2O$	C,H
11j	6-NMeAc	100	100–102	Et_2O	$C_{15}H_{17}NO_2$	C,H,N
11k	6-CF_3	100	65–70 (0.5)		$C_{13}H_{11}F_3O$	C,H
11l	6-CF_2CF_3	84	105–110 (0.9)		$C_{14}H_{11}F_5O$	C,H
11m	6,7-Cl_2	69	108	CH_2Cl_2	$C_{12}H_{10}Cl_2O$	C,H
11n	7-Br	71	100–105 (0.5)		$C_{12}H_{11}BrO$	C,H
12a	H	64	oil[c]		$C_{12}H_{12}O_2 \cdot 0.25H_2O$	C,H
12b	6-OMe	61	190–195 (0.5)		$C_{12}H_{14}O_3$	C,H
12c	6-F	86	oil[c]		$C_{12}H_{11}FO_2$	C,H
12d	6-Cl	55	85–86	CH_2Cl_2	$C_{12}H_{11}ClO_2 \cdot 0.5H_2O$	C,H
12e	6-Cl	55	85–86	CH_2Cl_2	$C_{12}H_{11}ClO_2 \cdot 0.5H_2O$	C,H
12e	6-Br	71	105	EtOAc	$C_{12}H_{11}BrO_2$	C,H
12f	6-CN	48	113–116	EtOAc	$C_{13}H_{11}NO_2 \cdot 0.5H_2O$	C,H,N
12i	6-SO_2Ph	50	56–58	Et_2O	$C_{17}H_{16}O_4S$	C,H
12j	6-NMeAc	71	129–131	EtOAc	$C_{15}H_{17}NO_3 \cdot 0.25H_2O$	C,H,N
12k	6-CF_3	53	51	EtOAc	$C_{13}H_{11}F_3O_2$	C,H
12l	6-CF_2CF_3	77	71–72	EtOAc	$C_{14}H_{11}F_5O_2$	C,H
12m	6,7-Cl_2	66	91–93	CH_2Cl_2	$C_{12}H_{10}Cl_2O_2 \cdot 0.25H_2O$	C,H
12n	7-Br	83	62–63	CH_2Cl_2	$C_{12}H_{11}BrO_2$	C,H
21a	H	53	114–115	EtOAc	$C_{12}H_{15}NO_2$	C,H
21b	6-OMe	76	99–104	EtOAc	$C_{12}H_{17}NO_3$	C,H
21c	6-F	61	113–117	EtOAc	$C_{12}H_{14}FNO_2$	C,H
21d	6-Cl	48	133	EtOAc	$C_{12}H_{14}ClNO_2$	C,H
21e	6-Br	78	125–126	EtOAc	$C_{12}H_{14}BrNO_2$	C,H
21f	6-CN	55	143–146	EtOAc	$C_{13}H_{14}N_2O_2 \cdot 0.25H_2O$	C,H,N
21j	6-NMeAc	58	112	CH_2Cl_2	$C_{15}H_{20}N_2O_3$	C,H,N
21n	7-Br	87	131	EtOAc	$C_{12}H_{14}BrNO_2$	C,H
23f	6-CN	82	214–215	EtOAc	$C_{19}H_{20}N_2O_4$	C,H,N

[a] Analyses for the elements indicated were within ±0.4% of the theoretical values. [b] C: found 76.89%, required 76.44%. [c] Decomposes on distillation.

28 was converted to its unsaturated analogue **37** by the acetylation–DBU procedure.

Other substituents at position 4 were introduced according to known procedures (Table IV). Thus, the 4-isoindolyl derivatives **38** were obtained upon treatment of **21e** and **21f** with 2-(bromomethyl)benzoate followed by *in situ* cyclization,[24] and cyanoacetamidine **40** was prepared from **21f** by reaction with ethyl *N*-cyanoacetimidate.[25]

Finally, the remaining 4-substituents were introduced by epoxide opening using different nucleophiles. Hence, reaction of **12e** with 2-(cyanoimino)imidazolidine or 2-(cyanoimino)thiazolidine (NaH, DMSO)[19] provided compounds **41** and **42**, respectively, with no trace of elimination products. Opening the epoxide **12f** with 1,3-cyclopentanedione (NaH, CuBr·Me_2S, DMSO)[26] resulted in low yields of compound **43**. Reaction of **12e** and **12f** with 3,6-pyridazinediol sluggishly afforded **44e** and **44f** as a result of an oxygen attack.[27] **44f** was selectively alkylated at the nitrogen atom to afford **45** and **46**. The elimination product **47** was obtained via the acetylation–DBU procedure.

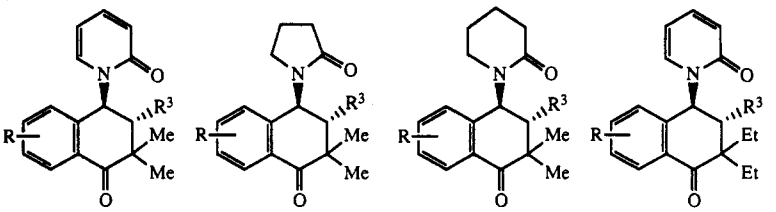
Position 1 of the 4-pyridones was modified as shown in Scheme IV (Table V). Reduction of **17e** with sodium borohydride in EtOH/THF afforded alcohol **48**, which was acetylated to give compound **49** and methylated to afford **50**. Tetralone **17e** was also reacted with methylmagnesium bromide to afford the 1-methyl-1-hydroxy derivative **51**. The oxime derivatives **52–53**, which consisted of mixtures of *E* and *Z* isomers, were obtained by reaction with the corresponding derivatized hydroxylamine hydrochlorides in the presence of pyridine in MeOH.

The synthesis of the 2,2-diethyl analogues was achieved following the route outlined in Scheme V. Diethylation of commercial 6-methoxy-1-tetralone **9b** afforded compound **54** which was demethylated using 48% hydrobromic acid to give phenol **55**. Reaction of **55** with triphenylphosphine dibromide at 200 °C[28] provided **57**, which was converted to the epoxide **59** following the aforementioned conditions. The opening of epoxide **59** with 2-pyridone in EtOH afforded directly the unsaturated compound **60e**, which was converted to **60f**. This shorter sequence also later proved to be much more useful in the dimethylated series, and it was used for large-scale syntheses.

Results and Discussion

Previous SAR studies on potassium channel activators typified by Cromakalim[6–13] have shown that the presence of both an electron-withdrawing group at the 6-position

Table II. Compounds 13, 15, 16, 17, 18, 19, 22, and 60



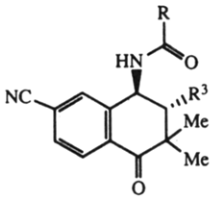
13, 15, 16, 17 18, 22 19 60

no.	R	R^3	mp, °C	recrystd solv	yield, % (method)	formula	anal.[b]	portal vein relaxation IC_{50},[c] μM	max. fall in BP[d] ± SEM, mmHg	tracheal relaxation IC_{50},[e] μM
13a	H	OH	263–265	M	13 (A)	$C_{17}H_{17}NO_3 \cdot 0.6H_2O$	C,H,N	NC (0)[f]	NS[g]	NT[h]
13b	6-OMe	OH	225	M	24 (A)	$C_{18}H_{19}NO_4$	C,H,N	NC (0)	42.9 ± 6.4	>10
13c	6-F	OH	254–257	MC	26 (A)	$C_{17}H_{16}FNO_3$	C,H,N	NC (0)	21.5 ± 6.5	NT
13d	6-Cl	OH	254–256	EA	32 (A)	$C_{17}H_{16}ClNO_3$	C,H,N	NC (0)	NT	NT
13e	6-Br	OH	250	E	51 (B)	$C_{17}H_{16}BrNO_3$	C,H,N	28	31.0 ± 7.7	>10
13f	6-CN	OH	244	MC	59 (A)	$C_{18}H_{16}N_2O_3$	C,H,N	14	84.0 ± 2.1	>10
13i	6-SO_2Ph	OH	186–190	EA	43 (B)	$C_{23}H_{21}NO_5S \cdot 0.25H_2O$	C,H,N	0.3	32.5 ± 6.4	0.7
13j	6-NMeAc	OH	180–184	EA	55 (B)	$C_{20}H_{22}N_2O_4 \cdot H_2O$	C,H,N	33	94.0 ± 10.0	>10
13k	6-CF_3	OH	202–205	EA	44 (B)	$C_{18}H_{16}F_3NO_3$	C,H,N	1.9	52.6 ± 8.8	1.4
13m	6,7-Cl_2	OH	190–192	EA	20 (A)	$C_{17}H_{15}Cl_2NO_3 \cdot 0.25H_2O$	C,H,N	1.5	52.0 ± 1.4	5.0
13n	7-Br	OH	191–192	EA	50 (A)	$C_{17}H_{16}BrNO_3$	C,H,N	42	29.3 ± 3.2	NT
15e	6-Br	OAc	225	E	61	$C_{19}H_{18}BrNO_4$	C,H,N	NC (38)	29.0 ± 4.9	NT
15f	6-CN	OAc	204	EA	85	$C_{20}H_{18}N_2O_4$	C,H,N[i]	23	64.7 ± 32.6	2.0
16f	6-CN	OCHO	191–193	EA	55	$C_{19}H_{16}N_2O_4 \cdot 0.25H_2O$	C,H,N	36	42.0 ± 5.0	4.3
17b	6-OMe	$\Delta^{3,4}$	164	EA	41 (D)	$C_{18}H_{17}NO_3$	C,H,N	21	42.5 ± 17.5	3.1
17c	6-F	$\Delta^{3,4}$	175–178	EA	72 (D)	$C_{17}H_{14}FNO_2$	C,H,N	19	35.0 ± 7.9	3.9
17d	6-Cl	$\Delta^{3,4}$	192.5	EA	71 (C)	$C_{17}H_{14}ClNO_2 \cdot 0.25H_2O$	C,H,N	1.4	53.7 ± 20.3	1.1
17e	6-Br	$\Delta^{3,4}$	172	EA	83 (C)	$C_{17}H_{14}BrNO_2$	C,H,N	0.5	42.6 ± 8.2[j]	0.2
17f	6-CN	$\Delta^{3,4}$	187	EA	63	$C_{18}H_{14}N_2O_2$	C,H,N	0.6	96.5 ± 17.3	0.5
17i	6-SO_2Ph	$\Delta^{3,4}$	83–90	EA	29 (E)	$C_{22}H_{19}NO_4S \cdot 0.25H_2O$	C,H,N	0.1	32.6 ± 7.7	0.5
17j	6-NMeAc	$\Delta^{3,4}$	160	EA	85 (C)	$C_{20}H_{20}N_2O_3$	C,H,N	4.3	74.0 ± 11.1	3.1
17k	6-CF_3	$\Delta^{3,4}$	130	EA	81 (D))	$C_{18}H_{14}F_3NO_2$	C,H,N	0.3	103.0 ± 2.8	0.5
17l	6-CF_2CF_3	$\Delta^{3,4}$	190	EA	71 (C)	$C_{19}H_{14}F_5NO_2$	C,H,N	I[k]	81.0 ± 13.7[j]	I[k]
17m	6,7-Cl_2	$\Delta^{3,4}$	213	EA	75 (D)	$C_{17}H_{13}Cl_2NO_2 \cdot 0.25H_2O$	C,H,N	0.7	58.0 ± 4.2	0.1
17n	7-Br	$\Delta^{3,4}$	194	EA	71 (D)	$C_{17}H_{14}BrNO_2 \cdot 0.25H_2O$	C,H,N	2.7	37.0 ± 9.3	4.7
17o	7-CN	$\Delta^{3,4}$	214	E	38	$C_{18}H_{14}N_2O_2$	C,H,N	NC (0)	41.0 ± 5.2	>10
17p	6-CCTMS	$\Delta^{3,4}$	84–94	EA	90	$C_{22}H_{23}NO_2Si \cdot 0.5H_2O$	C,H,N	0.5	91.5 ± 8.9	2.4
17q	6-CCH	$\Delta^{3,4}$	167–169	EA	74	$C_{19}H_{15}NO_2$	C,H,N	1.0	94.0 ± 21.9	0.2
17r	6-Et	$\Delta^{3,4}$	51–52	DE	74	$C_{19}H_{19}NO_2 \cdot 0.5H_2O$	C,H,N	5.5	58.0 ± 13.4	5.1
17s	6-CH=CH_2	$\Delta^{3,4}$	42–48	EA	74	$C_{19}H_{17}NO_2 \cdot 0.5H_2O$	C,H,N	1.5	30.6 ± 10.8	4.6
17t	6-COMe	$\Delta^{3,4}$	153–154	EA	45	$C_{19}H_{17}NO_3 \cdot 0.25H_2O$	C,H,N	3.3	56.5 ± 6.4	1.0
17u	6-C(NH)OMe	$\Delta^{3,4}$	198–200	EA	37	$C_{19}H_{18}N_2O_3 \cdot 0.5H_2O$	C,H,N	11	27.5 ± 13.8	3.1
17v	6-COOH	$\Delta^{3,4}$	293	EA	53	$C_{18}H_{15}NO_4 \cdot 0.75H_2O$	C,H,N	NC (0)	NS	>10
17w	6-COOMe	$\Delta^{3,4}$	188–189	EA	43	$C_{19}H_{17}NO_4 \cdot 0.5H_2O$	C,H,N	2.7	39.0 ± 16.0	8.5
17x	6-$CONH_2$	$\Delta^{3,4}$	168	DE	52	$C_{18}H_{16}N_2O_3 \cdot 0.5H_2O$	C,H,N	NC (21)	NS	>10
17y	6-NHMe	$\Delta^{3,4}$	116–120	EA	56	$C_{18}H_{18}N_2O_2 \cdot 0.25H_2O$	C,H,N	52	NS	9.1
18a	H	$\Delta^{3,4}$	135–136	EA	41	$C_{16}H_{17}NO_2$	C,H,N	NC (0)	NS	NT
18b	6-OMe	$\Delta^{3,4}$	100–101	E	32	$C_{17}H_{19}NO_3$	C,H,N	NC (20)	NS	NT
18d	6-Cl	$\Delta^{3,4}$	161–162	EA	48	$C_{16}H_{16}ClNO_2 \cdot 1H_2O$	C,H,N	NC (0)	32.5 ± 5.4	>10
18e	6-Br	$\Delta^{3,4}$	96	EA	26	$C_{16}H_{16}BrNO_2$	C,H,N	10	60.5 ± 7.5	7.3
18f	6-CN	$\Delta^{3,4}$	144	EA	83	$C_{17}H_{16}N_2O_2$	C,H,N	0.8	103.0 ± 32.9	0.9
18j	6-NMeAc	$\Delta^{3,4}$	166–168	EA	83	$C_{19}H_{22}N_2O_3 \cdot 0.5H_2O$	C,H,N	17	23.0 ± 5.9	2.5
18n	7-Br	$\Delta^{3,4}$	153–154	EA	79	$C_{16}H_{16}BrNO_2$	C,H,N[l]	NC (11)	54.5 ± 9.5	>10
18o	7-CN	$\Delta^{3,4}$	95–100	EA	46	$C_{17}H_{16}N_2O_2 \cdot 0.5H_2O$	C,H,N	NC (0)	24.5 ± 8.5	NT
19e	6-Br	$\Delta^{3,4}$	50–52	EA	23	$C_{17}H_{18}BrNO_2$	C,H,N	8.0	43.6 ± 13.3	3.5
22e	6-Br	OH	217	EA	63	$C_{16}H_{18}BrNO_3$	C,H,N	NC (40)	39.0 ± 9.0	>10
22f	6-CN	OH	268	EA	63	$C_{17}H_{18}N_2O_3$	C,H,N	NC (12)	23.0 ± 10.0	>10
60e	6-Br	$\Delta^{3,4}$	>300	EA	30	$C_{19}H_{18}BrNO_2 \cdot 0.5H_2O$	C,H,N	3.3	44.0 ± 8.8	8.0
60f	6-CN	$\Delta^{3,4}$	157	EA	58	$C_{20}H_{18}N_2O_2 \cdot 0.7H_2O$	C,H,N	7.8	35.6 ± 8.3	2.6
2								0.1	73.0 ± 11.3[j]	0.3

[a] EA = ethyl acetate; E = ethanol; M = methanol; MC = methylene chloride; DE = diethyl ether. [b] Analyses for the elements indicated were within ±0.4% of the theoretical values. [c] Drug concentration required to inhibit the noradrenaline-induced contractions in rat portal vein by 50%. Each value is the average of two or more preparations. [d] Changes in systolic blood pressure (mean ± SEM) measured at intervals of 1 h during 4 h after oral administration of 1 mg/kg of the compound in groups of four SHR. [e] Drug concentration required to inhibit spontaneous tone of guinea pig isolated tracheal spirals. Maximum relaxation was induced by isoprotenerol. Each value is the average of two or more preparations. [f] Not calculated. The percentage of inhibition at 10 μM is shown in parentheses. [g] Not significant (ΔBP < 20 mmHg). [h] Not tested. [i] H: found 7.52%, required 7.00%. [j] Dose of product: 0.1 mg/kg. [k] Insoluble. [l] C: found 58.10%, required 57.50%.

of the benzopyran nucleus and of a *gem*-dialkyl group (preferably methyl) at the 2-position are essential for good biological activity, while replacement of the benzopyran oxygen by NH, CH_2, or S has a detrimental effect. Five- and six-membered cyclic amides stand out among the substituents successfully introduced at the 4-position, and as for the 3-position either a *trans*-hydroxyl group or a double bond between positions 3 and 4 provide active compounds. We then envisaged a new modification of the benzopyran ring, involving substitution of the pyran oxygen by a carbonyl group. This change would significantly affect the electronic nature of the aromatic ring, but the spatial positions of the essential oxygen atom and the remaining key atoms of the molecule would mostly be

Table III. Acyclic Amides



no.	R	R^3	mp, °C	recryst solv[a]	yield, %	formula	anal.[b]	portal vein relaxation IC_{50},[c] μM	max. fall in BP[d] ± SEM, mmHg	tracheal relaxation IC_{50},[e] μM
24f	CH_3	OH	171–175	EA	81	$C_{15}H_{16}N_2O_3$	C,H,N	45	28.6 ± 9.9	8.7
28	2-pyridyl	OH	207–208	EA	82	$C_{19}H_{17}N_3O_3 \cdot 0.25H_2O$	C,H,N	23	71.7 ± 14.2	>10
29	3-pyridyl	OH	185–187	EA	70	$C_{19}H_{17}N_3O_3 \cdot 1H_2O$	C,H,N	2.8	50.0 ± 9.8	4.1
30	4-pyridyl	OH	223	EA	69	$C_{19}H_{17}N_3O_3$	C,H,N	NC[f] (39)	NS[g]	>10
31	3-furyl	OH	220–224	EA	67	$C_{18}H_{16}N_2O_4$	C,H,N	NC (24)	58.0 ● 17.5	NT[h]
32	phenyl	OH	230–234	MC	55	$C_{20}H_{18}N_2O_3 \cdot 0.5H_2O$	C,H,N	10	31.0 ± 11.9	1.8
33	4-$MeOC_6H_5$	OH	205–208	MC	54	$C_{21}H_{20}N_2O_3 \cdot 0.25H_2O$	C,H,N	12	46.7 ± 8.6	12.2
34	2,4-$Cl_2C_6H_4$	OH	100–104	EA	69	$C_{20}H_{16}Cl_2N_2O_3 \cdot 0.25H_2O$	C,H,N	NC(35)	NS	>10
35	3,4-$Cl_2C_6H_4$	OH	225–228	EA	95	$C_{20}H_{16}Cl_2N_2O_3 \cdot 0.5AcOEt$	C,H,N	NC(67)	NS	>10
36	4-$NO_2C_6H_5$	OH	249–250	EA	84	$C_{20}H_{17}N_3O_5$	C,H,N	4.9	NS	7.9
37	2-pyridyl	$\Delta^{3,4}$	148	EA	67	$C_{19}H_{15}N_3O_2$	C,H,N	9	22.5 ± 0.5	3.1

[a–h] See corresponding footnotes of Table II.

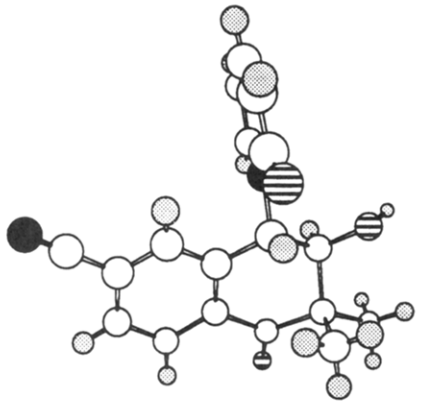


Figure 1. X-ray crystal structure of compound **13f**. White circles indicate carbon atoms, dotted circles hydrogen atoms, striped circles oxygen atoms, and black circles nitrogen atoms.

left unchanged. In fact, this was later confirmed by the X-ray crystal structure of compound **13f** (Figure 1), which like that described for its benzopyran analogue,[29] showed the 4-pyridone group orthogonal to the tetralone ring, and the amide oxygen on the same side of the tetralone ring as H_4. No intramolecular hydrogen bonding was observed, although the molecules are linked together in the crystal by intermolecular hydrogen bonds between the hydroxyl and the pyridone oxygen.

The vascular smooth muscle relaxant activity of the new compounds was evaluated in isolated rat portal vein precontracted with noradrenaline. Their *in vivo* activity as antihypertensives was determined after oral administration to conscious spontaneously hypertensive rats (SHR). The airway's smooth muscle relaxant activity was ascertained by measuring the spontaneous tone relaxation of isolated guinea pig tracheal spirals.

Taking into account the SAR studies of the benzopyran series, several positions of the tetralone nucleus were modified in order to identify the key features for achieving good vascular and airways activities.

We first focused our attention on the aromatic substituent. It is fairly evident from the results presented in Table II that its nature and position have a crucial effect upon activity. As shown in Figure 2, where the portal vein IC_{50} values are plotted against the sigma value (σ_p)[30] of the corresponding phenyl ring substituents, a rough

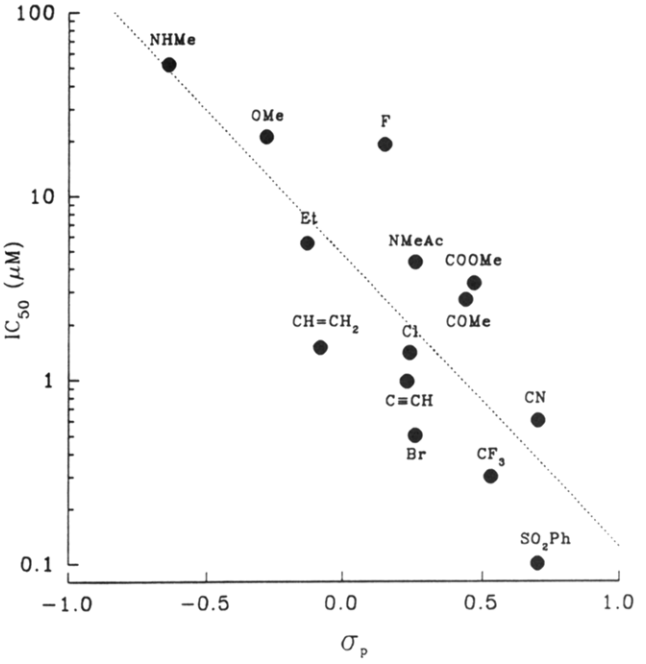
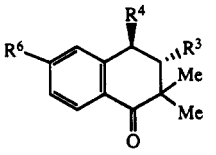
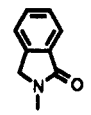
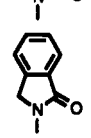
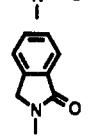
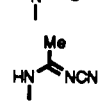
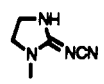
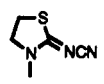
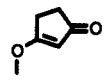
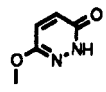
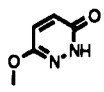
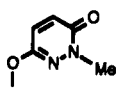
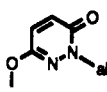
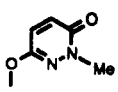


Figure 2. Variations of IC_{50} in micromolar (logarithmic scale) against σ_p of substituents at 6-position of compounds **17**. Regression parameters: $y = 14.1 - 29.3x$ ($r = 0.77$).

correlation between potency and the electronic nature of the substituents exists, whereby the most active compounds are those containing powerful electron-withdrawing substituents. Despite the major changes that conjugate CO causes on the π-aromatic system, these trends coincide to a large extent with those observed in the benzopyran series.[6c] Thus, in both the saturated and the unsaturated 4-pyridones and 4-pyrrolidones, the unsubstituted or 6-methoxy-substituted compounds showed little or no activity in the three tests. Halogen substituents, in turn, displayed increased potency in the order of their deactivating nature (F < Cl < Br). The 6-carbonitriles maintained (**17e** *vs* **17f**) or surpassed (**13e** *vs* **13f**; **18e** *vs* **18f**) the potency of their 6-bromo counterparts, while switching substitution to 7-position caused a substantial fall in activity. The 6,7-disubstituted derivatives **13m** and **17m**, on the contrary, showed good *in vitro* activities. For the 4-pyridones **17** a wider range of substituents was studied, showing that *in vitro* activity increases with the

Table IV. Variations at the 4-Position



no.	R^4	R^6	R^3	mp, °C	recryst solv[a]	yield, %	formula	anal.[b]	portal vein relaxation IC_{50},[c] μM	max. fall in BP[d] ± SEM, mmHg	tracheal relaxation IC_{50},[e] μM
14e		Br	OH	142–144	EA	22	$C_{17}H_{16}BrNO_3$	C,H,N	NC (32)[f]	33.0 ± 8.0	NT[g]
14f		CN	OH	156–158	EA	8	$C_{18}H_{16}N_2O_3 \cdot 0.25H_2O$	C,H,N	25	43.0 ± 16.0	5.5
38e		Br	OH	249–252	EA	37	$C_{20}H_{18}BrNO_3 \cdot 0.25H_2O$	C,H,N[h]	3.1	24.0 ± 5.6	>10
38f		CN	OH	199–202	EA	33	$C_{21}H_{18}N_2O_3 \cdot 0.75H_2O$	C,H,N	0.5	76.0 ± 11.4	1.1
39		CN	$\Delta^{3,4}$	160–162	EA	28	$C_{21}H_{16}N_2O_2 \cdot 0.25H_2O$	C,H,N	0.6	34.0 ± 13.0	1.3
40		CN	OH	207–209	EA	40	$C_{16}H_{16}N_4O_2 \cdot 0.25H_2O$	C,H,N	NC (19)	NS[i]	3.5
41		Br	OH	231	EA	13	$C_{16}H_{17}BrN_4O_2 \cdot 0.5H_2O \cdot EtOH$	C,H,N	NC (8)	27.6 ± 8.1	>10
42		Br	OH	241	EA	16	$C_{16}H_{16}BrN_3O_2S \cdot 1.25H_2O$	C,H,N	NC (26)	30.5 ± 13.7	NT
43		CN	OH	181	EA	4	$C_{18}H_{12}NO_4 \cdot 2.25H_2O$	C,H,N	NC (9)	50.0 ± 16.0	>10
44e		Br	OH	247–250	M	20	$C_{16}H_{15}BrN_2O_4 \cdot 0.25H_2O$	C,H,N	0.8	46.5 ± 0.3	4.4
44f		CN	OH	250–252	M	65	$C_{17}H_{15}N_3O_4$	C,H,N	8.8	116.0 ± 5.9	2.1
45		CN	OH	159	EA	66	$C_{18}H_{17}N_3O_4 \cdot 0.75H_2O$	C,H,N	2.8	112.0 ± 1.0	0.6
46		CN	OH	156–157	EA	76	$C_{20}H_{19}N_3O_4 \cdot 0.25H_2O$	C,H,N	14	20.5 ± 0.5	3.9
47		CN	$\Delta^{3,4}$	120–123	EA	95	$C_{17}H_{13}N_3O_3$	C,H,N	NC (0)	24.0 ± 2.8	NT

[a–f] See corresponding footnotes of Table II. [g] Not tested. [h] N: found 11.92%, required 11.37%. [i] Not significant (ΔBP < 20 mmHg).

presence of deactivating groups such as CN, CF_3, CF_2CF_3, or SO_2Ph in position 6. Nevertheless, the free carboxylic acid **17v** and the amide **17x** are totally inactive, as observed in the benzopyran series,[17] indicating that these polar groups are not tolerated at this position. In most cases the *in vivo* results are in keeping with those obtained in the portal vein test, although the intrinsically most active 6-phenylsulfonyl compounds **13i** and **17i** produced little change in the SHR's systolic blood pressure, probably due to a lack of oral bioavailability.

Once the major preferences had been established for this series, we sought to broaden our knowledge of the SAR with the 6-Br and 6-CN compounds and further study the effect of the remaining positions of the molecule.

As for the 4-position, the results from Table II show that, in general, the 4-pyridone compounds **13** and **17** were superior *in vitro* to their 4-pyrrolidone (**22** and **18**) and 4-piperidinone (**19**) counterparts. In all cases the activity of the unsaturated compounds was markedly superior to that of their *trans*-3-hydroxy analogues (**17** *vs* **13**, **18** *vs* **22**), a result similar to that observed in the 4-pyridonyl benzopyrans,[17] but different in the case of the saturated

Table V. Variations at the 1-Position for Compounds of Scheme IV

no.	mp, °C	recryst solv[a]	yield, %	formula	anal.[b]	portal vein relaxation IC_{50}, μM	max. fall in BP[d] ± SEM, mmHg	tracheal relaxation IC_{50},[e] μM
17e						0.5	42.6 ± 8.2[f]	0.2
17f						0.6	96.5 ± 17.3	0.5
49	204–206	EA	77	$C_{17}H_{16}BrNO_2$	C,H,N	NC (38)[g]	NS[h]	>10
50	194	EA	64	$C_{19}H_{18}BrNO_3$	C,H,N	NC (22)	28.0 ± 19.0	17
51	146–147	EA	53	$C_{18}H_{18}BrNO_2 \cdot 0.25H_2O$	C,H,N[i]	NC (23)	NS	4.2
52	93	EA	42	$C_{18}H_{18}BrNO_2$	C,H,N	NC (27)	28.0 ± 8.0	12.5
53	220–224	EA	51	$C_{18}H_{15}N_3O_2 \cdot 2H_2O$	C,H,N	25	32.4 ± 8.1	>10
54	158	EA	93	$C_{19}H_{17}N_3O_2 \cdot 1H_2O$	C,H,N	8.0	83.0 ± 10.2	>10

[a–e] See corresponding footnotes of Table II. [f] Dose of product: 0.1 mg/kg po. [g] Not calculated. The percentage of inhibition at 10 μM is shown in parentheses. [h] Not significant (ΔBP < 20 mmHg). [i] H: found 5.52%, required 5.04%.

amides, where both types of compounds are equipotent.[22] The 3-hydroxypyridone **13i** was the only compound which showed similar in vitro activities to its unsaturated analogue **17i** (compare, i.e., **13f**/**13i** *vs* **17f**/**17i**), although as mentioned earlier, both compounds were poorly active *in vivo*. Introduction of the 2,3-dihydro-1-oxo-1*H*-isoindol-2-yl radical present in Celikalim afforded compounds **38e** and **38f** (Table IV). The latter showed improved activity in the three tests compared to **22f**, while its unsaturated analogue **39** was devoid of action *in vivo*.

Position 4 was further modified by introducing acyclic amides to prepare compounds **24f** and **28–36** (Table III). Their overall activity was inferior to the 4-pyridones **13f** and **17f**, and only compound **28** showed promising antihypertensive potency. Unlike the cyclic amides, in this case the unsaturated derivative **37** showed poorer oral activity than did its hydroxylated analogue. In contrast to the results observed in the benzopyran series, where compounds **7** and **8** showed interesting activities, the (*N*-cyanoacetimidoyl)amino **40** (Table IV) showed no improvement over the activity of its acetamide analogue **24f**, and similarly, the cyanoimino derivatives **41** and **42** were poorly active.

As for the oxygen bonded radicals, the byproducts **14** showed little activity and in contrast to the benzopyran compound **5**, the (3-oxo-1-cyclopenten-1-yl)oxy derivative **43** was inactive. The (6-hydroxy-3-pyridazinyl)oxy radical, however, was well tolerated, and the carbonitrile **44f** in particular produced a maximum decrease in blood pressure in spite of its moderate activity as a portal vein relaxant. Methylation of **44f** afforded **45**, which showed increased *in vitro* activity and sustained potency *in vivo*, comparable with that described[27] for its benzopyran analogue **4**, while allylation produced a negative effect. In this case the unsaturated derivative **47** was devoid of activity, a result consistent with previous findings.[27]

The hydroxyl group at the 3-position was acylated (**15**, **16**, **23**) and oxidized (**20**) giving rise to less potent compounds. Similarly, the *cis*-3-hydroxy compound **27** was completely inactive.

Positions 1 and 2 of the 4-pyridones **17** were subsequently modified. Although the *N*-methoxyimino derivative **53** retained some oral activity, replacement of the carbonyl function by other oxygen containing groups led to significant loss in potency (Table V). As far as the size of the geminal group at the 2-position is concerned, the 2,2-diethyl group derivative showed significantly reduced potency, compared to its dimethyl analogue, in the three tests (Table II, **60** vs **17**).

In order to prove the *in vivo* activity one additional test was performed. On the one hand, the oral bronchodilatory activity of the more potent compounds in the tracheal test was evaluated by measuring the percentage

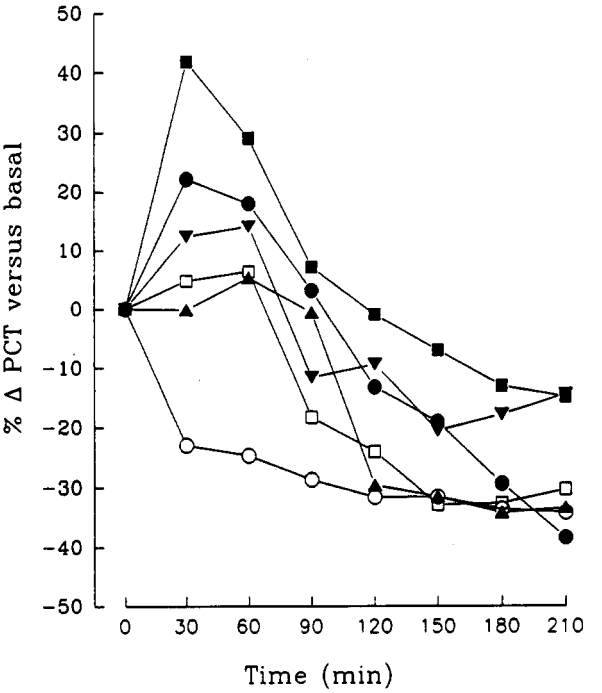


Figure 3. Percentage of increase of preconvulsive time (PCT) in an histamine induced bronchospasm after oral administration of vehicle (○), Levcromakalim (□), **17e** (▲), **17f** (●), **17k** (▼), and **17l** (■) at a dose of 1 mg/kg. Each data point represents the mean value derived from eight experiments.

Table VI. ED_{30} of Selected Compounds

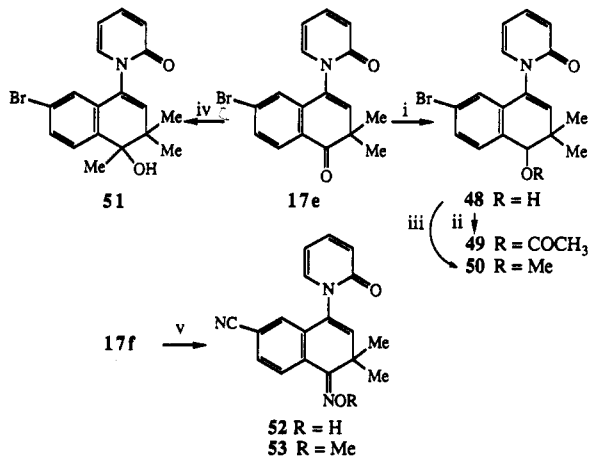
compd	ED_{30},[a] mg/kg po	compd	ED_{30},[a] mg/kg po
17e	0.009	**18f**	0.03
17f	0.004	**44f**	0.006
17k	0.005	**45**	0.04
17l	0.002	**1**	0.05
17p	0.005	**2**	0.01
17q	0.002		

[a] Dose required to decrease systolic blood pressure by 30 mmHg.

of preconvulsive time (PCT) increase in a histamine induced bronchospasm model after administration of 1 mg/kg of product to conscious guinea pigs.[31] While compounds **13i**, **17i**, **17m**, **17q**, and **45** were shown to be weakly or shortly active, compounds **17e**, **17f**, **17k**, and **17l** produced significant PCT increases, in the range of or superior to Levcromakalim **2** (Figure 3). The weak effect of **17q** and **45** in the PCT test compared to their antihypertensive action may be attributed to a lesser oral bioavailability in guinea pig compared to rat. Finally, the ED_{30} of the most potent antihypertensive compounds at the dose of 1 mg/kg was calculated (Table VI), showing that the group of unsaturated 4-pyridones contain the most active molecules, superior to reference compound **2**.

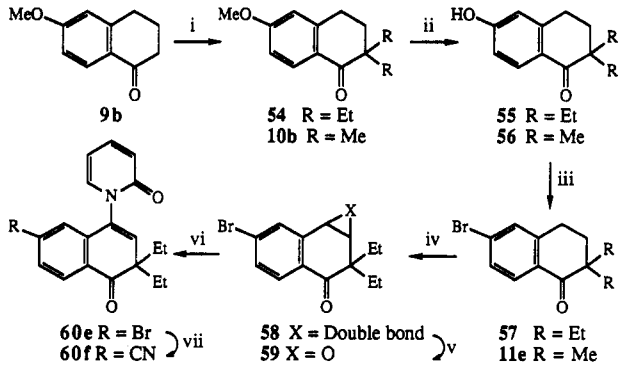
In summary, this study shows that substitution of the

Scheme IV[a]



[a] (i) $NaBH_4$, EtOH/THF; (ii) Ac_2O, pyridine; (iii) IMe, NaH, THF; (iv) MeMgI, THF; (v) NH_2OR·HCl, pyridine, MeOH, reflux.

Scheme V[a]



[a] (i) NaH, RI, PhH, reflux; (ii) 48% HBr, reflux; (iii) Br_2PPh_3, 200 °C; (iv) (1) NBS, CCl_4, 60 °C; (2) KOH, EtOH; (v) MCPBA, CH_2Cl_2; (vi) 2-pyridone, pyridine, EtOH, reflux; (vii) CuCN, NMP, reflux.

oxygen atom of the benzopyran ring, present in several current potassium channel openers, by a keto group leads to a similarly potent series and that the major SAR trends are mirrored in this π-extended system. The group of 1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethylnaphthalen-1-ones with an electron-withdrawing substituent at the 6-position contain the most active compounds, and 1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carbonitrile, **17f** (UR-8225), has been selected for further pharmacological development.

Experimental Section

A. Chemistry. Melting points were determined with a Mettler FP 80 central processor melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 983 spectrophotometer. ^1H (80-MHz) and ^{13}C (20.1-MHz) NMR spectra were recorded on a Brücker AC 80 spectrometer, and ^1H (500-MHz) NMR spectra were recorded on a VXR-500 spectrometer; they are reported in ppm on the δ scale, from the indicated reference. Combustion analyses were performed with a Carlo Erba 1106 analyzer. Liquid chromatography was performed with a forced flow (flash chromatography) of the indicated solvent system on SDS silica gel Chromagel 60 A.C.C. (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed with Macherey-Nagel 0.25-mm silica gel SIL G-25 plates. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran (THF), diethyl ether, and toluene were distilled from sodium metal/benzophenone ketyl. Dichloromethane, triethylamine, and *N*-methylpyrrolidone (NMP) were distilled from calcium hydride. Chloroform was passed through an alumina column.

Compound **2** was kindly provided by SmithKline Beecham.

6-Bromo-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-one (10e). To a solution of 6-bromo-1,2,3,4-tetrahydronaphthalen-1-one (**9e**)[14c] (49.2 g, 0.22 mol) and IMe (40.7 mL, 0.65 mol) in PhH (170 mL) was added, under an argon atmosphere, 55% NaH (19.0 g, 0.44 mol). The mixture was stirred at 60 °C for 5 h and then at reflux overnight. The suspension was poured into MeOH, and the solvent was removed. The residue was dissolved in Et_2O and washed with H_2O and 10% Na_2CO_3 solution. The organic phase was dried over $MgSO_4$, and the solvent was evaporated. The residue was purified by flash chromatography (hexane–CH_2Cl_2) to afford compound **10e** as an oil (44.0 g, 80%): bp 155–160 °C (0.5 mmHg); ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.90 (d, J = 9 Hz, 1H, Ar), 7.39 (m, 2H, Ar), 2.96 (t, J = 6.5 Hz, 2H, CH_2Ar), 1.96 (t, J = 6.5 Hz, 2H, CH_2), 1.20 (s, 6H, 2 CH_3). Anal. ($C_{12}H_{13}BrO$) C, H.

2,2-Dimethyl-6-(phenylthio)-1,2,3,4-tetrahydronaphthalen-1-one (10h). A mixture of **10e** (1.83 g, 7.2 mmol), thiophenol (0.77 mL, 7.60 mmol), and K_2CO_3 (2.48 g, 18.07 mmol) in NMP (18.6 mL) was stirred at 160 °C under a nitrogen atmosphere overnight. The mixture was poured into a H_2O–Et_2O (1:1, 80 mL) mixture, and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with 5% NaOH solution and with H_2O and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH_2Cl_2) to afford compound **10h** as an oil (1.66 g, 81%): bp 220–225 °C (0.5 mmHg); ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.90 (d, J = 8.7 Hz, 1H, Ar), 7.41 (m, 5H, Ar), 7.05 (d, J = 8.7 Hz, 1H, Ar), 6.99 (s, 1H, Ar), 2.88 (t, J = 6.5 Hz, 2H, CH_2Ar), 1.93 (t, J = 6.5 Hz, 2H, CH_2), 1.19 (s, 6H, 2 CH_3). Anal. ($C_{18}H_{18}OS$) C, H, S.

2,2-Dimethyl-1,2,3,4-tetrahydro-6-(trifluoromethyl)naphthalen-1-one (10k). To a solution of **10e** (1.85 g, 7.3 mmol) in NMP (50 mL) were added, under an argon atmosphere, CuI (5.5 g, 29 mmol) and sodium trifluoroacetate (3.94 g, 29 mmol), and the mixture was stirred for 48 h at 160 °C. The solution was poured into a mixture of H_2O (600 mL) and Et_2O (600 mL). The layers were separated, and the aqueous phase was extracted with Et_2O. The combined organic phases were washed with H_2O and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH_2Cl_2) to afford compound **10k** as an oil which solidified after distillation (1.05 g, 59%): bp 80–85 °C (0.5 mmHg); mp 28–30 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.14 (d, J = 8.6 Hz, 1H, Ar), 7.53 (m, 2H, Ar), 3.05 (t, J = 6.4 Hz, 2H, CH_2Ar), 2.01 (t, J = 6.4 Hz, 2H, CH_2), 1.23 (s, 6H, 2 CH_3). Anal. ($C_{13}H_{13}F_3O$) C, H.

6-Bromo-1,2-dihydro-2,2-dimethylnaphthalen-1-one (11e). A mixture of **10e** (44.0 g, 0.17 mol), NBS (40.0 g, 0.22 mol), and benzoyl peroxide (0.65 g) in CCl_4 (312 mL) was stirred for 5 h at reflux. The imide formed was filtered, and the solvent was evaporated to yield a residue that was treated with 10% KOH (10 mL) in EtOH at 45 °C for 1 h. After removal of the solvent, the residue was dissolved in Et_2O, washed with H_2O and 5% Na_2CO_3 solution, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH_2Cl_2) to afford **11e** as an oil which solidified after distillation (41.7 g, 74%): bp 115–120 °C (0.5 mmHg); mp 49–52 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.90 (d, J = 8 Hz, 1H, Ar), 7.45 (m, 2H, Ar), 6.44 (d, J = 9.6 Hz, 1H, CHAr), 6.14 (d, J = 9.6 Hz, 1H, CH), 1.28 (s, 6H, 2 CH_3). Anal. ($C_{12}H_{11}BrO$) C, H.

1,2-Dihydro-2,2-dimethyl-1-oxonaphthalene-6-carbonitrile (11f). A mixture of **10f** (2.84 g, 0.014 mol), NBS (3.24 g, 0.018 mol), and benzoyl peroxide (0.08 g) in CCl_4 (55 mL) was stirred for 5 h at reflux. The imide formed was filtered, and the solvent was evaporated to provide a residue that was treated with DBU (2.2 mL, 0.014 mol) and heated at 85 °C for 30 min. The mixture was dissolved in Et_2O, washed with H_2O and 5% Na_2CO_3 solution, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH_2Cl_2) to afford **11f** as a white solid, which was recrystallized from CH_2Cl_2 (1.92 g, 68%): mp 104–105 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.12 (d, J = 8.5 Hz, 1H, Ar), 7.58 (m, 2H, Ar), 6.47 (d, J = 9.6 Hz, 1H, CHAr), 6.19 (d, J = 9.6 Hz, 1H, CH), 1.32 (s, 6H, 2 CH_3). Anal. ($C_{13}H_{11}NO$) C, H, N.

6-Bromo-2,2-dimethyl-3,4-epoxy-1,2,3,4-tetrahydronaphthalen-1-one (12e). To a solution of **11e** (41.7 g, 0.17 mol) in

CH_2Cl_2 (270 mL) was added 50% *m*-chloroperbenzoic acid (51.9 g, 0.17 mol) dissolved in CH_2Cl_2 (100 mL), and the resulting mixture was stirred overnight at room temperature. The resulting suspension was filtered, and the filtrates were washed successively with 10% $Na_2S_2O_5$ and saturated $NaHCO_3$ solutions and dried over $MgSO_4$. The solvent was removed to yield 50 g of a residue that was purified by flash chromatography (hexane–EtOAc) to afford **12e** as a white solid, which was recrystallized from EtOAc (31.5 g, 71%): mp 105 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.76 (m, 3H, Ar), 3.99 (d, J = 4 Hz, 1H, CHAr), 3.57 (d, J = 4 Hz, 1H, CH), 1.50 (s, 3H, CH_3), 1.13 (s, 3H, CH_3). Anal. ($C_{12}H_{11}BrO_2$) C, H.

***trans*-6-Bromo-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-3-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (13e). Method A.** A mixture of **12e** (0.5 g, 1.87 mmol), pyridine (0.15 mL, 1.87 mmol), and 2-hydroxypyridine (0.36 g, 2.7 mmol) in EtOH (3 mL) was stirred at reflux for 2 days. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc). The more polar fractions afforded **13e** as a white solid, which was recrystallized from EtOH (0.30 g, 44%): mp 250 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.96 (m, 1H, Ar), 7.54 (m, 3H, Ar), 7.2–6.2 (m, 4H, Ar + CHN), 4.05 (s, H_2O + OH), 3.95 (d, J = 8 Hz, 1H, CHOH), 1.38 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). Anal. ($C_{17}H_{16}BrNO_3$) C, H, N.

The less polar fractions yielded *trans*-6-bromo-4-(2-pyridyloxy)-2,2-dimethyl-3-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (**14e**) as a yellowish solid which was recrystallized from EtOAc (0.065 g, 10%): mp 142–144 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.19 (m, 2H, Ar), 7.70 (m, 3H, Ar), 7.34 (m, 1H, Ar), 7.05 (m, 1H, Ar), 6.25 (d, J = 8.8 Hz, 1H, CHO), 4.8 (br s, 1H, OH), 4.02 (d, J = 8.8 Hz, 1H, CHOH), 1.41 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). Anal. ($C_{17}H_{16}BrNO_3$) C, H, N.

Method B. To a solution of **12e** (0.5 g, 1.87 mmol) in THF (7 mL) was added, under an argon atmosphere, 2-[(trimethylsilyl)oxy]pyridine (0.62 g, 3.7 mmol). The mixture was cooled to 0 °C, and $Bu_4NF{\cdot}3H_2O$ (0.88 g, 2.8 mmol) was added. After being stirred for 5 days at room temperature, the mixture was poured into H_2O, and the aqueous phase was extracted with EtOAc. The solution was dried over $MgSO_4$, and the solvent was removed to afford a residue that was treated with CH_2Cl_2. The suspension obtained was filtered to provide 0.100 g of **13e**. The filtrate was purified by flash chromatography (hexane–EtOAc) to give 0.25 g more of product (total yield: 51%) and 0.15 g of **14e** (22%).

***trans*-3-Acetoxy-6-bromo-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1,2,3,4-tetrahydronaphthalen-1-one (15e).** A mixture of **13e** (0.490 g, 1.4 mmol), Ac_2O (2.7 mL, 28 mmol), and pyridine (5.4 mL) was stirred at room temperature for 18 h. The solvent was removed, and the residue was redissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$, and the solvent was removed to afford 0.650 g of a residue that was purified by flash chromatography (hexane–EtOAc) to yield **15e** as a white solid, which was recrystallized from EtOH (0.33 g, 61%): mp 225 °C; ^1H NMR (80 MHz, CD_3OD) δ (TMS) 7.96 (m, 1H, Ar), 7.8–7.2 (m, 3H, Ar), 7.1–6.2 (m, 4H, Ar + CHN), 5.64 (d, J = 10.4 Hz, 1H, CHO), 1.98 (s, 3H, CH_3CO), 1.33 (s, 3H, CH_3), 1.26 (s, 3H, CH_3). Anal. ($C_{19}H_{18}BrNO_4$) C, H, N.

6-Bromo-1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethylnaphthalen-1-one (17e). Method C. To a solution of **15e** (0.200 g, 0.49 mmol) in PhMe (3 mL) was added dropwise, under an argon atmosphere, DBU (0.09 mL, 0.6 mmol), and the mixture was stirred at reflux overnight. The solvent was removed, and the residue was redissolved in EtOAc. The solution was washed with H_2O and dried over $MgSO_4$. The solvent was removed to afford a residue that was purified by flash chromatography (hexane–EtOAc) to yield **17e** as a white solid, which was recrystallized from EtOAc (0.14 g, 83%): mp 172 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.99 (d, J = 8 Hz, 1H, Ar), 7.50 (m, 2H, Ar), 7.23 (d, J = 6.4 Hz, 1H, Ar), 6.98 (d, J = 2 Hz, 1H, Ar), 6.67 (d, J = 8 Hz, 1H, Ar), 6.34 (m, 1H, Ar), 6.23 (s, 1H, CH), 1.44 (s, 3H, CH_3), 1.38 (s, 3H, CH_3). Anal. ($C_{17}H_{14}BrNO_2$) C, H, N.

Method D. A mixture of **13e** (5.0 g, 13.8 mmol), NaOH/silica (Merck 1567, 4.2 g), and dioxane (220 mL) was stirred for 30 min at reflux. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to yield **17e** (3.67 g, 77%).

Method E. To a solution of **12e** (20.0 g, 75 mmol) in THF (280 mL) was added, under an argon atmosphere, 2-[(trimethylsilyl)oxy]pyridine (35.0 g, 150 mmol). The mixture was cooled to 0 °C, and $Bu_4NF{\cdot}3H_2O$ (24.0 g, 75 mmol) was added. After being stirred for one night at reflux, the mixture was poured into H_2O and the aqueous phase was extracted with EtOAc. The solution was dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc) to give **17e** (13.5 g, 51%) and **14e** (8.0 g, 29%).

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carbonitrile (17f). A mixture of **13e** (1.55 g, 4.2 mmol), CuCN (0.56 g, 6.1 mmol), and NMP (9.5 mL) was stirred under an argon atmosphere for 2.5 h at reflux. The mixture was poured into a 10% ethylenediamine solution, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with H_2O and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to give the product as a white solid, which was recrystallized from EtOAc (0.75 g, 63%): mp 187 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.20 (d, J = 8 Hz, 1H, Ar), 7.60 (m, 2H, Ar), 7.20 (m, 2H, Ar), 6.69 (d, J = 8 Hz, 1H, Ar), 6.30 (m, 1H, Ar), 6.30 (s, 1H, CH), 1.47 (s, 3H, CH_3), 1.40 (s, 3H, CH_3). Anal. ($C_{18}H_{14}N_2O_2$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-[(trimethylsilyl)ethynyl]naphthalen-1-one (17p). To a solution of **17e** (1 g, 2.9 mmol) in deaerated, anhydrous NEt_3 (6.5 mL) was added, under an argon atmosphere, PPh_3 (0.022 g, 0.084 mmol), palladium(II) acetate (0.0009 g, 0.035 mmol), and ethynyltrimethylsilane (0.65 mL, 4.5 mmol), and the mixture was stirred overnight at reflux. The precipitated triethylamine hydrobromide was filtered, and the brown filtrate was concentrated. The residue was mixed with saturated $NaHCO_3$ solution and CH_2Cl_2, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, and the solvent was removed. The resulting crude product was purified by flash chromatography (hexane–EtOAc) to give **17p** as a white solid, which was recrystallized from ethyl acetate (0.950 g, 90%), mp 84–94 °C. Anal. ($C_{22}H_{23}NO_2Si{\cdot}0.5H_2O$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-ethynylnaphthalen-1-one (17q). A mixture of **17p** (0.68 g, 1.9 mmol), K_2CO_3 (0.024 g, 0.17 mmol), and MeOH (5 mL) was stirred for 3 h at room temperature. The solvent was concentrated, and the residue was mixed with a saturated $NaHCO_3$ solution and CH_2Cl_2. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, and the solvent was removed. The resulting residue was purified by flash chromatography (hexane–EtOAc) to afford **17q** as a white solid, which was recrystallized from EtOAc (0.405 g, 74%): mp 167–169 °C. Anal. ($C_{19}H_{15}NO_2$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-ethylnaphthalen-1-one (17r). A mixture of **17q** (0.15 g, 0.51 mmol) and 5% Pd/C (0.03 g) in EtOAc (9 mL) was hydrogenated at atmospheric pressure for 2 h. After filtration, the solvent was removed to provide **17r** as a white solid, which was recrystallized from ether (0.11 g, 74%): mp 51–52 °C. Anal. ($C_{19}H_{19}NO_2{\cdot}0.5H_2O$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-ethenylnaphthalen-1-one (17s). A mixture of **17q** (0.20 g, 0.69 mmol), 5% Pd on $CaCO_3$ (0.008 g), and a drop of quinoline in EtOH (1.4 mL) was hydrogenated at atmospheric pressure for 40 min. After filtration, the solvent was removed to afford **17s** as a white solid, which was recrystallized from EtOAc (0.13 g, 74%): mp 42–48 °C. Anal. ($C_{19}H_{17}NO_2{\cdot}0.5H_2O$) C, H, N.

6-Acetyl-1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethylnaphthalen-1-one (17t). A mixture of **17q** (0.20 g, 0.69 mmol) and $Hg(OAc)_2$ (0.434 g, 1.36 mmol) in AcOH (0.7 mL) was stirred at room temperature for 4 days. After more $Hg(OAc)_2$ was added (0.200 g), stirring was continued for 2 additional days. The solution was treated with thioacetamide (0.1 g, 1.36 mmol) and the mixture stirred for 3 h. The suspension thus obtained was treated with Et_2O and filtered. The solid was washed with EtOAc, and the combined organic phases were washed with H_2O and dried over $MgSO_4$. The solvent was removed to afford a residue that was purified by flash chromatography (hexane–EtOAc) to give **17t** as a white solid, which was

recrystallized from EtOAc (0.095 g, 45%): mp 153–154 °C. Anal. ($C_{19}H_{17}NO_3 \cdot 0.25H_2O$) C, H, N.

Methyl 1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carboximidate (17u). To a solution of **17f** (0.290 g, 1 mmol) in MeOH (2 mL) was added, under an argon atmosphere, NaOMe (0.020 g, 0.38 mmol), and the mixture was stirred overnight at room temperature. A drop of AcOH was added to the solution, and it was poured into H_2O (5 mL) and extracted with EtOAc. The solution was dried over $MgSO_4$, and the solvent was removed. The residue thus obtained was purified by flash chromatography (hexane–EtOAc) to give 0.150 g of starting product and **17u** as a white solid, which was recrystallized from EtOAc (0.130 g, 37%): mp 198–200 °C. Anal. ($C_{19}H_{18}N_2O_3 \cdot 0.5H_2O$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carboxylic Acid (17v). A suspension of **17f** (0.250 g, 0.86 mmol) in 6 N HCl (2 mL) was stirred overnight at reflux. After cooling, H_2O (5 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic phase was extracted with 1 N NaOH, and the basic aqueous phase was acidified and extracted with CH_2Cl_2. The solution was dried over $MgSO_4$ and the solvent was removed to afford **17v** as a white solid, which was recrystallized from EtOAc (0.140 g, 53%): mp 293 °C. Anal. ($C_{18}H_{15}NO_4 \cdot 0.75H_2O$) C, H, N.

Methyl 1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carboxylate (17w). HCl gas was passed through a boiling solution of **17f** (0.75 g, 2.6 mmol) in MeOH (7 mL) over 4.5 h, and the mixture was left to stand overnight. The solvent was removed, and H_2O (5 mL) was added to the residue. The mixture was extracted with $CHCl_3$, and the solution was dried over $MgSO_4$. The solvent was removed, and the resulting residue was purified by flash chromatography (hexane–EtOAc) to give **17w** as a white solid, which was recrystallized from EtOAc (0.36 g, 43%): mp 188–189 °C. Anal. ($C_{19}H_{17}NO_4 \cdot 0.5H_2O$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-oxonaphthalene-6-carboxamide (17x). To a suspension of KOH (0.48 g, 8.5 mmol) in *tert*-butyl alcohol (4 mL) was added **17f** (0.250 g, 0.86 mmol), and the mixture was stirred for 1 h at reflux. The solvent was removed, H_2O (5 mL) was added to the residue, and the mixture was extracted with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated to give **17x** as a white solid, which was recrystallized from ether (0.14 g, 52%): mp 168 °C. Anal. ($C_{18}H_{16}N_2O_3 \cdot 0.5H_2O$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-(methylamino)naphthalen-1-one (17y). A solution of **17j** (0.15 g, 1.5 mmol) in 6 N HCl (3 mL) was heated at reflux for 2 h. The mixture was allowed to cool and was poured into 4 N NaOH and extracted with EtOAc. The solution was dried over $MgSO_4$, and the solvent was removed. The residue thus obtained was recrystallized from EtOAc to give **17y** as a white solid (0.25 g, 56%): mp 116–120 °C. Anal. ($C_{18}H_{18}N_2O_2 \cdot 0.25H_2O$) C, H, N.

6-Bromo-1,2-dihydro-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-naphthalen-1-one (18e) and 6-Bromo-2,2-dimethyl-4-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthalene-1,3-dione (20e). To a suspension of 55% NaH (0.088 g, 2.0 mmol) and DMSO (2 mL) was added 2-pyrrolidone (0.16 mL, 2.0 mmol), and the mixture was stirred for 15 min under an argon atmosphere. The epoxide **12e** (0.5 g, 1.9 mmol) in DMSO (2 mL) was added to the suspension, and the mixture was stirred at room temperature overnight. The resulting solution was poured into H_2O (100 mL) and extracted with EtOAc. The organic phase was washed with H_2O and dried over $MgSO_4$. The solvent was removed, and the residue purified by flash chromatography (hexane–EtOAc). The more polar fractions afforded **18e** as a white solid, which was recrystallized from EtOAc (0.16 g, 26%): mp 96 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.94 (d, J = 8 Hz, 1H, Ar), 7.53 (dd, J = 8 Hz, J = 1.9 Hz, 1H, Ar), 7.26 (d, J = 1.9 Hz, 1H, Ar), 6.13 (s, 1H, CH), 3.69 (t, J = 7.1 Hz, 2H, CH_2N), 2.58 (m, 2H, CH_2CO), 2.31 (m, 2H, CH_2), 1.35 (s, 6H, 2 CH_3). Anal. ($C_{16}H_{16}BrNO_2$) C, H, N.

The less polar fractions afforded **20e** as a white solid (0.13 g, 20%): mp 145–147 °C: ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.23 (m, 1H, Ar), 7.94 (m, 2H, Ar), 5.29 (s, 1H, CHN), 3.52 (m, 2H, CH_2N), 2.6–1.9 (m, 4H, 2 CH_2), 1.35 (s, 3H, CH_3), 1.29 (s, 3H, CH_3). Anal. ($C_{16}H_{16}BrNO_3$) C, H, N.

***trans*-4-Amino-6-bromo-2,2-dimethyl-3-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (21e).** A mixture of **12e** (1.0 g, 3.7 mmol), 30% aqueous NH_3 (5 mL), and EtOH (10 mL) was stirred at reflux for 2 days. The solvent was removed, and the residue was dissolved in 1 N HCl and washed with Et_2O. The aqueous phase was basified with 1 N NaOH and extracted with Et_2O. The organic phase was dried over $MgSO_4$, and the solvent was removed, affording a residue that was purified by flash chromatography (hexane–EtOAc) to provide **21e** as a white solid, which was recrystallized from EtOAc (0.83 g, 78%): mp 125–126 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.91 (d, J = 8 Hz, 1H, Ar), 7.53 (m, 1H, Ar), 7.36 (m, 1H, Ar), 3.94 (d, J = 9.9 Hz, 1H, CHN), 3.44 (d, J = 9.9 Hz, 1H, CHO), 2.38 (s, 3H, NH_2 + OH), 1.37 (s, 3H, CH_3), 1.13 (s, 3H, CH_3). Anal. ($C_{12}H_{14}BrNO_2$) C, H, N.

***trans*-6-Bromo-2,2-dimethyl-3-hydroxy-4-(2-oxo-1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthalen-1-one (22e).** To a solution of **21e** (0.88 g, 0.003 mol) and NEt_3 (0.43 mL, 3 mmol) in $CHCl_3$ (40 mL) was added 4-chlorobutyryl chloride (0.432 g, 3 mmol), and the mixture was stirred for 1 h at room temperature. The organic phase was washed with H_2O and dried over $MgSO_4$. The solvent was removed and the residue purified by flash chromatography (hexane–EtOAc) to yield *trans*-6-bromo-4-[(4-chlorobutyryl)amino]-2,2-dimethyl-3-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one as a white solid (1.34 g, 100%): mp 86–90 °C; ^1H NMR (80 MHz, CD_3OD) δ (TMS) 7.89 (d, J = 8.9 Hz, 1H, Ar), 7.54 (m, 2H, Ar), 5.28 (d, J = 9.9 Hz, 1H, CHN), 3.69 (t, J = 6.1 Hz, 2H, CH_2Cl), 3.65 (d, J = 9.9 Hz, 1H, CHO), 2.58 (m, 4H, CH_2CO + OH + NH), 2.21 (m, 2H, CH_2), 1.33 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). Anal. ($C_{16}H_{19}BrClNO_3$) C, H, N.

A mixture of the previous product (1.10 g, 2.8 mmol), K_2CO_3 (9.04 g, 65 mmol), and KI (0.94 g, 5.7 mmol) in acetone (200 mL) was stirred at reflux for 24 h. The solvent was removed and the residue redissolved in H_2O and extracted with $CHCl_3$. The organic phase was dried over $MgSO_4$, and the solvent was removed. The resulting residue was purified by flash chromatography (hexane–EtOAc) to afford **22e** as a white solid, which was recrystallized from EtOAc (0.63 g, 63%): mp 217 °C; ^1H NMR (80 MHz, CD_3OD) δ (TMS) 7.92 (d, J = 8.3 Hz, 1H, Ar), 7.60 (m, 1H, Ar), 7.34 (m, 1H, Ar), 5.38 (d, J = 10.3 Hz, 1H, CHN), 4.73 (s, H_2O + OH), 3.92 (d, J = 10.3 Hz, 1H, CHO), 3.46 (t, J = 7.6 Hz, 2H, CH_2N), 2.62 (m, 2H, CH_2CO), 2.17 (m, 2H, CH_2), 1.33 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). Anal. ($C_{16}H_{18}BrNO_3$) C, H, N.

***trans*-4-(Acetylamino)-2,2-dimethyl-3-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (24f).** To a solution of **21f** (0.20 g, 0.9 mmol) and NEt_3 (0.12 mL, 0.9 mmol) in $CHCl_3$ (9 mL) was added acetyl chloride (0.06 mL, 0.9 mmol), and the mixture was stirred for 30 min at room temperature. The organic phase was washed with H_2O and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to afford **24f** as a white solid, which was recrystallized from EtOAc (0.22 g, 81%): mp 171–175 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.14 (d, J = 8 Hz, 1H, Ar), 7.69 (m, 2H, Ar), 6.02 (d, J = 8 Hz, 1H, NH), 5.34 (t, J = 9.6 Hz, 1H, CHN), 3.76 (d, J = 9.6 Hz, 1H, CHO), 2.22 (s, 3H, CH_3), 2.0 (br, s, 1H, OH), 1.36 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). Anal. ($C_{15}H_{16}N_2O_3$) C, H, N.

5-Bromo-2,9,9-trimethyl-8-oxo-1a,3a,8,9-tetrahydronaphthaleno[1,2-*d*]oxazoline (25). To a solution of **24e** (0.50 g, 1.5 mmol) in CH_2Cl_2 (24 mL) was added, under an argon atmosphere, (diethylamino)sulfur trifluoride, DAST (0.20 mL, 1.6 mmol), and the mixture was stirred for 2 h at room temperature. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to provide **25** as a white solid (0.38 g, 82%): mp 119–120 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.9–7.4 (m, 3 H, Ar), 5.16 (d, J = 8 Hz, 1H, CHN), 4.68 (d, J = 8 Hz, 1H, CHO), 1.91 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.18 (s, 3H, CH_3). Anal. ($C_{14}H_{14}BrNO_2$) C, H, N.

***cis*-4-Amino-6-bromo-2,2-dimethyl-3-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (26).** A mixture of **25** (2.62 g, 8.5 mmol) and 3 N HCl (86 mL) was refluxed for 3 h. After cooling, the solution was extracted with Et_2O. The aqueous phase was basified with 2 N NaOH and extracted with EtOAc. The solution was dried over $MgSO_4$, and the solvent was removed to give **26** as a white solid (1.4 g, 58%): mp 198 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.0–7.6 (m, 3 H, Ar), 4.31 (d, J = 2.4 Hz, 1H,

CHN), 3.82 (d, J = 2.4 Hz, 1H, CHO), 1.35 (s, 3H, CH_3), 1.18 (s, 3H, CH_3). Anal. ($C_{12}H_{14}BrNO_2$) C, H, N.

***trans*-2,2-Dimethyl-3-hydroxy-1-oxo-4-[(2-pyridylcarbonyl)amino]-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (28).** A mixture of **21f** (0.20 g, 0.9 mmol), DCC (0.176 g, 0.9 mmol), 2-picolinic acid (0.107 g, 0.9 mmol), and 1-hydroxybenzotriazole (0.116 g, 0.9 mmol) in anhydrous DMF (2.5 mL) was stirred for 18 h at room temperature under an argon atmosphere. The suspension was poured into EtOAc and filtered. The filtrate was washed with saturated $NaHCO_3$ solution and H_2O and dried over $MgSO_4$. The solvent was removed and the residue purified by flash chromatography (hexane–EtOAc) to afford **28** as a white solid, which was recrystallized from EtOAc (0.24 g, 82%): mp 207–208 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.53 (m, 2H, Ar), 8.19 (m, 2H, Ar), 8.1–7.6 (m, 4 H, Ar + NH), 5.55 (t, J = 9.6 Hz, 1H, CHN), 3.97 (d, J = 9.6 Hz, 1H, CHO), 3.0 (br s, 1H, OH), 1.40 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). Anal. ($C_{19}H_{17}N_3O_3 \cdot 0.25H_2O$) C, H, N.

***trans*-4-(2,3-Dihydro-1-oxo-1*H*-isoindol-2-yl)-2,2-dimethyl-3-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (38f).** A mixture of **21f** (0.66 g, 2.9 mmol), methyl 2-(bromomethyl)benzoate (0.66 g, 2.9 mmol), K_2CO_3 (1.16 g, 8.4 mmol), and KI (0.233 g, 1.4 mmol) in CH_3CN (16 mL) was stirred at reflux under a nitrogen atmosphere for 24 h. The cooled mixture was vacuum filtered through Celite. The precipitate was washed with EtOAc, and the filtrates were combined and evaporated. The residue was dissolved in EtOAc, washed with H_2O and 0.1 N $Na_2S_2O_3$, and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to afford **38f** as a white solid, which was recrystallized from EtOAc (0.36 g, 33%): mp 199–202 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.21 (d, J = 8 Hz, 1H, Ar), 8.0–7.3 (m, 6H, Ar), 5.68 (d, J = 10.4 Hz, 1H, CHN), 4.9–4.1 (m, 2H, CHO + OH), 3.08 (s, 2H, CH_2), 1.42 (s, 3H, CH_3), 1.26 (s, 3H, CH_3). Anal. ($C_{21}H_{18}N_2O_3 \cdot 0.75H_2O$) C, H, N.

***trans*-4-[(*N*-Cyanoacetimidoyl)amino]-2,2-dimethyl-3-hydroxy-1-oxo-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (40).** A mixture of ethyl *N*-cyanoacetimidate (0.54 g, 4.8 mmol) and **21f** (0.20 g, 0.9 mmol) was stirred at 100 °C overnight. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to yield **40** as a white solid, which was recrystallized from EtOAc (0.10 g, 40%): mp 207–209 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.84 (m, 1H, NH), 8.15 (d, J = 8 Hz, 1H, Ar), 7.71 (m, 2 H, Ar), 5.39 (m, 1H, CHN), 4.17 (s, 1H, OH), 3.80 (d, J = 9.6 Hz, 1H, CHO), 2.49 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.19 (s, 3H, CH_3). Anal. ($C_{16}H_{16}N_4O_2 \cdot 0.25H_2O$) C, H, N.

***trans*-6-Bromo-4-[2-(cyanoimino)thiazolidin-3-yl]-2,2-dimethyl-3-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (42).** To a suspension of 55% NaH (0.088 g, 2.0 mmol) in DMSO (2 mL) was added 2-(cyanoimino)thiazolidine (0.26 g, 2.0 mmol), and the mixture was stirred for 15 min under an argon atmosphere. The epoxide **12e** (0.5 g, 1.9 mmol) in DMSO (2 mL) was added to the suspension, and the mixture was stirred at room temperature overnight. The resulting solution was poured into H_2O (100 mL) and extracted with EtOAc. The organic phase was washed with H_2O and dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to yield **42** as a white solid (0.12 g, 16%) together with 0.25 g of the starting epoxide. One sample was recrystallized from EtOAc: mp 241 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.97 (d, J = 8 Hz, 1H, Ar), 7.60 (dd, J = 8 Hz, J = 1.9 Hz, 1H, Ar), 7.31 (d, J = 1.9 Hz, 1H, Ar), 5.74 (d, J = 11 Hz, 1H, CHN), 4.1–3.3 (m, 5H), 3.0 (wide signal, 1H, OH), 1.39 (s, 3H, CH_3), 1.19 (s, 3H, CH_3). Anal. ($C_{16}H_{16}BrN_3O_2S \cdot 1.25H_2O$) C, H, N.

***trans*-2,2-Dimethyl-3-hydroxy-1-oxo-4-[(3-oxo-1-cyclopent-1-enyl)oxy]-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (43).** To a solution of 1,3-cyclopentanedione (0.38 g, 3.9 mmol) in anhydrous THF (37 mL) was added, under an argon atmosphere, 55% NaH (0.166 g, 3.5 mmol). After 30 min, CuBr·Me_2S (0.70 g, 3.5 mmol) was added, followed by a solution of epoxide **12f** (0.5 g, 2.3 mmol) in anhydrous THF (6 mL). The mixture was stirred at room temperature for 15 days, and the solvent was removed. The residue was partitioned between $CHCl_3$ and H_2O, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc) to yield starting epoxide (0.30 g, 60%) and **43** as a white solid (0.030 g, 4%): mp 181 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.20 (d, J = 8 Hz, 1H, Ar), 7.76 (m, 2H, Ar), 5.68 (s, 1H, CH=), 5.42 (d, J = 8 Hz, 1H, CHO), 4.08 (d, J = 8 Hz, 1H, CHOH), 2.70 (m, 5H, 2 CH_2 + OH), 1.39 (s, 3H, CH_3), 1.27 (s, 3H, CH_3). Anal. ($C_{18}H_{17}NO_4 \cdot 2.25H_2O$) C, H, N.

***trans*-2,2-Dimethyl-3-hydroxy-4-[(6-hydroxy-3-pyridazinyl)oxy]-1-oxo-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (44f).** A mixture of **12f** (0.5 g (2.3 mmol), 3,6-dihydroxypyridazine (0.25 g, 2.3 mmol), and pyridine (0.18 mL, 2.3 mmol) in EtOH (4.2 mL) was stirred at reflux under an argon atmosphere for 2 days. The solvent was removed to afford a residue that was treated with CH_2Cl_2. The resulting suspension was filtered to give **44f** as a white solid, which was recrystallized from MeOH (0.50 g, 65%): mp 250–252 °C; ^{1}H NMR (80 MHz, $CDCl_3$–CD_3OD) δ (TMS) 8.16 (d, J = 8 Hz, 1H, Ar), 7.78 (m, 2H, Ar), 7.22 (d, J = 9.6 Hz, 1H, pyr), 7.02 (d, J = 9.6 Hz, 1H, pyr), 6.17 (d, J = 8 Hz, 1H, CHO), 4.01 (d, J = 8 Hz, 1H, CHOH), 3.68 (s, 2H, OH + NH), 1.36 (s, 3H, CH_3), 1.25 (s, 3H, CH_3). Anal. ($C_{17}H_{15}N_3O_4$) C, H, N.

***trans*-2,2-Dimethyl-3-hydroxy-4-[(6-hydroxy-1-methyl-3-pyridazinyl)oxy]-1-oxo-1,2,3,4-tetrahydronaphthalene-6-carbonitrile (45).** A mixture of **44f** (0.32 g, 0.98 mmol), K_2CO_3 (0.98 g, 7.1 mmol), IMe (0.44 mL, 7.1 mmol), and acetone (15 mL) was stirred under an argon atmosphere for 3 h. The solvent was removed and the residue partitioned between $CHCl_3$ and H_2O. The aqueous phase was extracted with $CHCl_3$, and the combined organic extracts were dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to yield **45** as a white solid, which was recrystallized from EtOAc (0.22 g, 66%): mp 159 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.19 (d, J = 8 Hz, 1H, Ar), 7.75 (m, 2H, Ar), 7.06 (s, 2H, pyr), 6.19 (d, J = 8.8 Hz, 1H, CHO), 4.06 (d, J = 8.8 Hz, 1H, CHOH), 3.68 (s, 3H, CH_3), 2.0 (br s, 1H, OH), 1.42 (s, 3H, CH_3), 1.28 (s, 3H, CH_3). Anal. ($C_{18}H_{17}N_3O_4 \cdot 0.75H_2O$) C, H, N.

6-Bromo-1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethylnaphthalen-1-ol (48). To a solution of **17e** (0.220 g, 0.64 mmol) in EtOH/THF (3:1, 4 mL) was added, under an argon atmosphere, $NaBH_4$ (0.05 g, 1.26 mmol), and the mixture was stirred for 2 h. The solvent was removed and the residue extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to an oil, which was purified by flash chromatography (hexane–EtOAc) to yield **48** as a white solid, which was recrystallized from EtOAc (0.170 g, 77%): mp 204–206 °C; ^{1}H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.30 (m, 4H, Ar), 6.69 (m, 2H, Ar), 6.27 (m, 1H, Ar), 5.85 (s, 0.5H, 0.5 CH=), 5.81 (s, 0.5H, 0.5 CH=), 4.53 (s, 0.5H, CH_{eq}–OH), 4.23 (s, 0.5H, CH_{ax}–OH), 3.52 (br s, 1H, OH), 1.29 (s, 1.5H, 0.5 CH_3), 1.17 (s, 1.5H, 0.5 CH_3), 1.04 (s, 1.5H, 0.5 CH_3), 0.95 (s, 1.5H, 0.5 CH_3). Anal. ($C_{17}H_{16}BrNO_2$) C, H, N.

6-Bromo-1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-methoxynaphthalene (50). To a suspension of 55% NaH (0.027 g, 0.54 mmol) in anhydrous THF (2 mL) were added **48** (0.15 g, 0.43 mmol) and IMe (0.15 g, 1.1 mmol), and the mixture was stirred under a nitrogen atmosphere overnight. The solvent was removed, and the residue was redissolved in Et_2O and washed with saturated $NaHCO_3$ solution and H_2O. The organic phase was dried over $MgSO_4$, and the solvent was removed to afford a residue that was purified by flash chromatography (hexane–EtOAc). The product **51** was obtained after recrystallization from EtOAc as a white solid (0.080 g, 53%): mp 146–147 °C; ^{1}H NMR (80 MHz, CD_3OD) δ (TMS) 7.6–6.9 (m, 4H, Ar), 6.83 (d, J = 1.7 Hz, 1H, Ar), 6.63 (d, J = 9.6 Hz, 1H, Ar), 6.22 (td, J = 6.4 Hz, J = 1.7 Hz, 1H, Ar), 5.88 (s, 1H, CH=), 4.10 (s, 0.74H, CHOMe), 3.93 (s, 0.26H, CHOMe), 3.47 (s, 0.74 × 3H, CH_3), 3.38 (s, 0.26 × 3H, CH_3), 1.23 (s, 3H, CH_3), 1.10 (s, 3H, CH_3). Anal. ($C_{18}H_{18}BrNO_2 \cdot 0.25H_2O$) C, H, N.

6-Bromo-1,2-dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-1,2,2-trimethylnaphthalen-1-ol (51). To a suspension of Mg (0.070 g, 3 mmol) in anhydrous Et_2O (1 mL) was added dropwise, under an argon atmosphere, a solution of IMe (0.09 mL, 1.4 mmol) in Et_2O (2 mL) so that a gentle reflux was observed. Then, a solution of **17e** (0.3 g, 0.9 mmol) in anhydrous THF (3 mL) was added, and the mixture was stirred for 1 h at room temperature and at reflux overnight. The resulting suspension was poured into H_2O and the mixture acidified with 1 N H_2SO_4 solution. The phases

were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc) to afford **51** as a white solid, which was recrystallized from EtOAc (0.130 g, 42%): mp 93 °C; ^1H NMR (80 MHz, CD_3OD) δ (TMS) 7.6–6.9 (m, 3H, Ar), 6.65 (m, 3H, Ar), 6.27 (m, 1H, Ar), 5.90 (s, 0.34H, CH=), 5.85 (s, 0.66H, CH=), 2.03 (br s, 1H, OH), 1.7–1.0 (m, 9H, 3 CH_3). Anal. ($C_{18}H_{18}BrNO_2$) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-1-(*N*-methoxyimino)naphthalene-6-carbonitrile (53). A mixture of **17f** (0.100 g, 0.34 mmol), $MeONH_2$·HCl (0.034 g, 0.41 mmol), pyridine (0.07 mL), and MeOH (1 mL) was stirred at reflux for 18 h. After additional $MeONH_2$·HCl (0.070 g, 0.82 mmol) was added, the mixture was stirred for 48 h and the solvent was removed. The residue was partitioned between $CHCl_3$ and H_2O, and the aqueous phase was extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, and the solvent was removed. The residue was purified by flash chromatography (hexane–EtOAc) to yield **53** as a white solid, which was recrystallized from EtOAc (0.100 g, 93%): mp 158 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 8.39 (d, J = 8 Hz, 0.5H, Ar), 8.24 (d, J = 8 Hz, 0.5H, Ar), 7.6–6.7 (m, 4H, Ar), 5.65 (d, J = 9 Hz, 1H, Ar), 6.27 (t, J = 6.4 Hz, 1H, Ar), 6.11 (s, 0.5H, 0.5 CH=), 5.73 (s, 0.5H, 0.5 CH=), 4.04 (s, 1.5H, 0.5 OCH_3), 3.98 (s, 1.5H, 0.5 OCH_3), 1.64 (s, 1.5H, 0.5 CH_3), 1.59 (S, 1.5H, 0.5 CH_3), 1.44 (s, 1.5H, 0.5 CH_3), 1.26 (s, 1.5H, 0.5 CH_3). Anal. ($C_{19}H_{17}N_3O_2$·H_2O) C, H, N.

2,2-Diethyl-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (55). A mixture of **54** (12.56 g, 0.054 mol, $bp_{0.5}$ 130–140 °C, prepared from **9b** and IEt as described for **10e**) and 48% HBr (150 mL) was heated under reflux for 3 h and distilled for 3 h more. The mixture was poured into H_2O and extracted with Et_2O. The organic phase was extracted with 1 N NaOH. The aqueous phase was acidified with 1 N HCl and extracted with Et_2O. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to afford **55** as a white solid, which was recrystallized from EtOAc (6.47 g, 55%): mp 125–126 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.96 (d, J = 8.4 Hz, 1H, Ar), 6.75 (d, J = 8.4 Hz, 1H, Ar), 6.66 (s, 1H, Ar), 2.90 (t, J = 6.3 Hz, 2H, CH_2Ar), 1.99 (t, J = 6.3 Hz, 2 H, CH_2), 1.62 (m, 5H, 2 CH_2CH_3 + OH), 0.84 (t, J = 7.3 Hz, 6H, 2 CH_3).

Via the same procedure but starting from **10b**, 2,2-dimethyl-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (**56**) was obtained as a white solid, which was recrystallized from ether (yield 72%): mp 141 °C. Anal. ($C_{12}H_{14}O_2$·$0.1H_2O$) C, H.

6-Bromo-2,2-diethyl-1,2,3,4-tetrahydronaphthalen-1-one (57). A mixture of **55** (5.30 g, 0.024 mol) and triphenylphosphonium dibromide (13.93 g, 0.033 mol) was stirred at 185 °C for 6 h. The black suspension thus obtained was poured into a mixture of H_2O and EtOAc, and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over $MgSO_4$. The solvent was removed, and the residue was purified by flash chromatography (hexane–EtOAc) to give **57** as a white solid (3.80 g, 56%): mp 49–53 °C; ^1H NMR (80 MHz, $CDCl_3$) δ (TMS) 7.89 (d, J = 8.9 Hz, 1H, Ar), 7.37 (m, 2H, Ar), 2.94 (t, J = 6.4 Hz, 2H, CH_2Ar), 2.00 (t, J = 6.4 Hz, 2H, CH_2), 1.61 (m, 4H, 2 CH_2CH_3), 0.84 (t, J = 7.5 Hz, 6H, 2CH_3).

Via the same procedure but starting from 2,2-dimethyl-6-hydroxy-1,2,3,4-tetrahydronaphthalen-1-one (**56**), the 6-bromo derivative **10e** was obtained (yield: 35%).

Crystal data for 13f: $C_{18}H_{16}N_2O_3$; M = 308.34; monoclinic; $P2_1/n$ (C^5_{2v}, no. 14); a = 917.3(8) pm; b = 1818.2(2) pm; c = 923.5(8) pm; α = 90°; β = 100.29°; γ = 90°; V = 1515.6 × 10^6 pm^3; Z = 4; ρ_x = 1.3513 $g \cdot cm^{-3}$; μ(Cu Kα) = 7.22 cm^{-1}; no. of reflections with $I \geq 3\sigma(I)$ = 2714; no. of refinement parameters = 225; final R values R = 0.043; R_w = 0.051.

B. Biological Methods. Inhibition of Noradrenaline-Induced Contractions in Isolated Rat Portal Vein. Portal vein was extracted from adult male rats (bw 200–250 g), that had been stunned and exanguinated. Vein strips were suspended in an isolated organ bath (Letica) containing a physiological saline solution continuously bubbled with 5% CO_2, 95% O_2 gas at 37 °C, pH 7.2. Contractions were induced by noradrenaline (3 μM) and were reverted after thorough washing with physiological saline solution (PSS: 117.9 mM NaCl, 25 mM $NaHCO_3$, 4.7 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgCl_2$, 11.1 mM glucose). Portal vein contraction was measured with an isometric force transducer at an initial tension of 1 g. After two equal contractions with noradrenaline, performed in order to measure the tissue's basal response, the test compounds dissolved in PSS were incubated for 30 min and a new contraction was induced. The concentration that produces a 50% inhibition (IC_{50}) versus the basal response was calculated. The experiment was repeated at least two times and the mean was calculated.

Lowering of the Arterial Pressure in Conscious Spontaneously Hypertensive Rats. Spontaneously hypertensive male rats (bs 200–250 g) were used. Diastolic and systolic arterial pressure were measured at the caudal artery using a sphygnomanometer (Letica 5007 and 5007/4) attached to the animal's tail. To ensure rapid and reliable data, animals were placed on a heating plate at 37 °C, with the aim of producing a vasodilatation that ensured better fixation of the rat tail to the transducer chamber. During the experiment, rats were conscious and fixed by a clamp. The test products suspended in 1% Tween 80 were administered orally. Arterial pressure was measured every 60 min over a period of 4 h and 10 min before the administration of the test compound. The drop in the arterial pressure was calculated for each compound at a dose of 1 mg/kg, using at least four animals. For the compounds which proved active at the 1 mg/kg dose, two to four additional doses were tested and the ED_{30} (dose required to reduce the blood pressure by 30 mmHg) was calculated from a linear regression of effect *vs* log dose.

Direct Relaxation of Isolated Guinea Pig Tracheal Spirals. Tracheae were extracted from male guinea pigs (bw 400 g) that had been stunned and exanguinated. Then, tracheae were cut in zigzag sections and placed in an isolated organ bath (Letica) containing Krebs-Henseleit solution at 37 °C, pH 7.4, continuously bubbled with carbogen (95% O_2 and 5% CO_2). The relaxation of the tracheae was measured using an isometric force transducer. The basal tension was 0.5 g. The test compounds dissolved in PSS were cumulatively added to the bath, and the effective concentration that produced 50% of the maximum relaxation (EC_{50}) was calculated. The maximum relaxation was taken to be the relaxation induced by isoproterenol at 1×10^{-6} M. The experiment was repeated at least two times, and the mean was calculated.

Inhibition of Histamine-Induced Bronchoconstriction in Conscious Guinea Pigs. Male guinea pigs were placed in a clear container of 15-L capacity and challenged with an aerosol generated from a 1% solution of histamine using an ultrasonic Devilbiss nebulizer. The period of exposure to the histamine aerosol, *i.e.* preconvulsive time (PCT),[34] until appearance of the first deep abdominal spasm was measured, and the animals were then removed from the container. The compounds and the vehicle (1% Tween 80) were orally administered at a dose of 1 mg/kg, and PCT was reassessed at 30-min intervals for up to 210 min. Eight animals were used per compound.

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Supplementary Material Available: X-ray crystallographic data, including positional parameters, bond distances, bond angles and anisotropic displacement parameter expressions for **13f** and ^1H-NMR spectral data of compounds **17p–y** (12 pages). Ordering information is given on any current masthead page.

References

(1) Cook, N. S. The Pharmacology of Potassium Channels and their Therapeutic Potential. *Trends Pharm. Sci.* 1988, *9*, 21–28.
(2) Dyson, J. The Markets for Potassium Channel Modulators. *Current Drugs: Potassium Channel Modulators* 1991, KCM-B93.
(3) Weston, A. H. New Developments in Potassium-Channel Pharmacology. *DN&P* 1988, *1*, 205–209.

(4) Edwards, G.; Weston, A. H. Structure-activity Relationships of K^+ Channel Openers. *Trends Pharm. Sci.* **1990**, *11*, 417–422.
(5) *Current Drugs. Potassium Channel Modulators* **1991**, A1–A25.
(6) (a) Robertson, D. W.; Steinberg, M. I. Potassium Channel Modulators: Scientific Applications and Therapeutic Promise. *J. Med. Chem.* **1990**, *33*, 1529–1541. (b) Attwood, M. R. Benzopyrans with Unsaturated 6-Membered Cyclicamido Substituents. *Current Drugs: Potassium Channel Modulators* **1991**, KCM-B39. (c) McCaully, R. J. Variations on the Benzopyran Nucleus. *Current Drugs* KCM-B5.
(7) Smith, D. G. 4-Amido-3,4-dihydro-2H-1-benzothiopyran-3-ols and their Sulphoxide and Sulphone Derivatives-Cromakalim Analogues. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3187–3191.
(8) Burrel, G.; Cassidy, F.; Evans, J. M.; Lightowler, D.; Stemp, G. Variation in the Aromatic Ring of Cromakalim: Antihypertensive Activity of Pyranopyridines and 6-Alkyl-2*H*-1-benzopyrans. *J. Med. Chem.* **1990**, *33*, 3023–3027.
(9) Sanfilippo, P. J.; McNally, J. J.; Press, J. B.; Fitzpatrick, L. J.; Urbanski, M. J.; Katz, L. B.; Giardino, E.; Falotico, R.; Salata, J.; Moore, J. B.; Miller, W. Thiophene Systems. 14. Synthesis and Antihypertensive Activity of Novel 7-(Cyclic amido)-6-hydroxythieno[3,2-b]pyrans and Related Compounds as New Potassium Channel Activators. *J. Med. Chem.* **1992**, *35*, 4425–4433.
(10) Ashwood, V. A.; Cassidy, F.; Evans, J. M.; Gagliardi, S.; Stemp, G. Synthesis and Antihypertensive Activity of Pyran Oxygen and Amide Nitrogen Replacement Analogues of the Potassium Channel Activator Cromakalim. *J. Med. Chem.* **1991**, *34*, 3261–3267.
(11) Buckle, D. R.; Eggleston, D. S.; Houge-Frydrych, C. S. V.; Pinto, I.; Readshaw, S. A.; Smith, D. G.; Webster, R. A. B. Conformational and Steric Modifications of the Pyran Ring of the Potassium-Channel Activator Cromakalim. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2763–2771.
(12) Matsuhisa, A.; Asano, M.; Matsumoto, Y.; Takayama, K.; Yoden, T.; Tsusuki, R.; Uchida, W.; Yanagisawa, I. Benzoxazine Derivatives, Their Preparation and Pharmaceutical Compositions Containing Them. European Patent Appl. EP 432893.
(13) (a) Baumgarth, M.; Gericke, R.; Bergmann, R.; de Peyer, J.; Lues, I. New 4-heterocyclyl-2H-1,3-benzoxazine Derivatives. European Patent Application EP 371312. (b) Shiraishi, M.; Hashiguchi, S.; Watanabe, T. New Potassium Channel Activating 1,3-Benzoxazine Derivatives. European Patent Application EP 477789.
(14) Buckle, D. R.; Arch, J. R. S.; Edge, C.; Foster, K. A.; Houge-Frydrych, C. S. V.; Pinto, I.; Smith, D. G.; Taylor, J. F.; Taylor, S. G.; Tedder, J. M.; Webster, R. A. B. Synthesis and Smooth Muscle Relaxant Activity of a New Series of Potassium Channel Activators: 3-Amido-1,1-dimethylindan-2-ols. *J. Med. Chem.* **1991**, *33*, 919–926.
(15) (a) Almansa, C.; Gómez, L. A.; Cavalcanti, F. L.; Carceller, E.; Bartroli, J.; García Rafanell, J.; Forn, J. 1-Naphthalenone potassium channel activators. I. Synthesis and effect of the phenyl ring substituents. XIIth International Symposium on Medicinal Chemistry, Basel, Switzerland, Sept 1992. (b) Almansa, C.; Gómez, L. A.; Cavalcanti, F. L.; Carceller, E.; Bartroli, J.; García Rafanell, J.; Forn, J. 1-Naphthalenone potassium channel activators. II. Structural modifications at the 1, 2 and 4 positions. XIIth International Symposium on Medicinal Chemistry, Basel, Switzerland, Sept 1992. (c) Rodríguez, R.; Cavalcanti, F. L.; Gómez, L. A.; García-Rafanell, J.; Forn, J. Los efectos vasorelajantes de los derivados de naftalenona UR-8225 y UR-8255 están mediados por canales de K+ sensibles a ATP. *Rev. Farm. Clini. Exp.* **1992**, Num esp, 289. (d) Casis, O.; Pérez-Vizcaino, F.; Rodríguez, R.; Gómez, L. A.; García-Rafanell, J.; Tamargo, J. Effects of the novel potassium channel opener UR-8225 on isolated rat vascular smooth muscle. *Br. J. Pharmacol.* **1993**, *108*, 182P.
(16) (a) R = 6-F, 6-CN, 6-$NHCOCH_3$: Allinger, N. L.; Jones, E. S. Synthesis of Some Functionally Substituted Benzocyclanones. *J. Org. Chem.* **1962**, *27*, 70–76. (b) R = 6-Cl: Hamilton, R. W. The antiarrhythmic and Antiinflamatory Activity of a Series of Tricyclic Pyrazoles. *J. Heterocycl. Chem.* **1976**, *13*, 545–553. (c) R = 6-Br: Itoh, K.; Miyake, A.; Tada, N.; Hirata, M.; Oka, Y. Synthesis and β-adrenergic Blocking Activity of 2-(N-Substitutedamino)-1,2,3,4-tetrahydronaphthalen-1-ol Derivatives. *Chem. Pharm. Bull.* **1984**, *32*, 130–151. (d) R = 6,7-Cl_2: Rosowsky, A.; Chaykovsky, M.; Yeager, S. A.; St. Amand, R. A.; Lin, M.; Modest, E. J. 7-Benz[c]acridinemethanol as Tetracyclic Analogs of the 2-Phenyl-4-quinolinemethanol Antimalarials. *J. Heterocycl. Chem.* **1971**, *8*, 809–820. (e) R = 7-Br: Griffin, R. W.; Gass, J. D.; Berwick, M. A.; Shulman, R. S. 1-Methyl-7-halo-2-naphthalenecarboxylic Acid Derivatives. *J. Org. Chem.* **1964**, *29*, 2109–2116.
(17) Bergmann, R.; Gericke, R. Synthesis and Antihypertensive Activity of 4-(1,2-Dihydro-2-oxo-1-pyridyl)-2H-1-benzopyrans and Related Compounds, New Potassium Channel Activators. *J. Med. Chem.* **1990**, *33*, 492–504.
(18) Englert, H. C.; Mania, D.; Schölkens, B.; Utz, R. European Patent Appl. EP 337179.
(19) Shiokawa, Y.; Takimoto, K.; Takenaka, K.; Kato, T. Benzopyran Derivatives and Processes for Preparation Thereof. European Patent Appl. EP 344747.
(20) Ellis, G. P.; Rommey-Alexander, T. M. Cyanation of Aromatic Halides. *Chem. Rev.* **1987**, *87*, 779–794.
(21) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. Facile Synthesis of Ethynylated Benzoic Acid Derivatives and Aromatic Compounds via Ethynyltrimethylsilane. *J. Org. Chem.* **1981**, *46*, 2280–2286.
(22) 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)-2H-1-benzopyrans. *J. Med. Chem.* **1986**, *29*, 2194–2201.
(23) Burrel, G.; Evans, J. M.; Jones, G. E.; Stemp, G. The Action of Diethylaminosulphur trifluoride (DAST) on Trans-4-amido-3-chromanols: Preparation of Cis-amidoalcohols Via Oxazolines. *Tetrahedron Lett.* **1990**, *31*, 3649–3652.
(24) Quagliato, D. A.; Humber, L. G.; Joslyn, B. L.; Soll, R. M.; Browne, E. N. C.; Shaw, C.; Van Engen, D. The Synthesis and Structural Characterization of WAY-120,491; A Novel Potassium Channel Activator. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 39–42.
(25) Ohtuka, K.; Ishiyama, N.; Iida, Y.; Seri, K.; Murai, T.; Sanai, K.; Ishizaka, Y. Benzopyran Compounds, Processes for Their Production and Pharmaceutical Compositions. European Patent Appl. EP 412531.
(26) Blarer, S. Benzo(6)pyrans and Pyranopyridines. UK Patent Appl. GB 2204868.
(27) Bergmann, R.; Eiermann, V.; Gericke, R. 4-Heterocyclyloxy-2H-1-benzopyran Potassium Channel Activators. *J. Med. Chem.* **1990**, *33*, 2759–2767.
(28) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. Studies in Organophosphorous Chemistry. I. Conversion of Alcohols and Phenols to Halides by Tertiary Phosphine Dihalides. *J. Am. Chem. Soc.* **1964**, *86*, 964–965.
(29) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. 3-Methyl-2H-1-benzopyran Potassium Channel Activators. *J. Med. Chem.* **1991**, *34*, 3074–3085.
(30) σ_p values taken from: Chapman, N. B.; Shorter, J. In *Correlation Analysis in Chemistry. Recent Advances*; Plenum Press: New York, 1979; pp 439–540.
(31) Paciorek, P. M.; Cowlrick, I. S.; Perkins, R. S.; Taylor, J. C.; Wilkinson, G. F.; Waterfall, J. F. Evaluation of the Bronchodilator Properties of Ro 31-6930, a Novel Potassium Channel Opener, in the Guinea-pig. *Br. J. Pharmacol.* **1990**, *100*, 289–294.