

2,2-Dialkyl-naphthalen-1-ones as New Potassium Channel Activators

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Received February 8, 1993

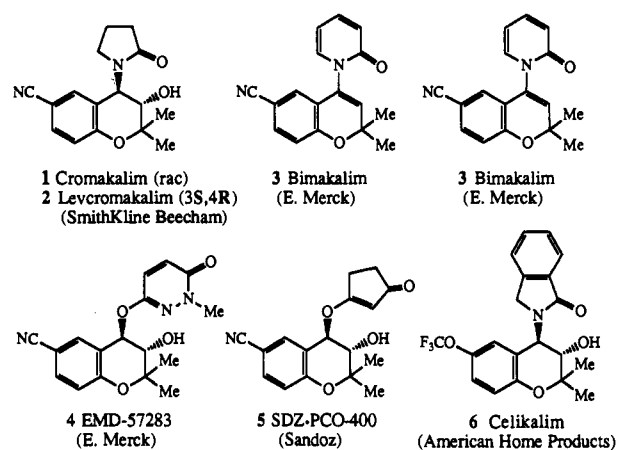
A new series of 2,2-dialkyl-naphthalen-1-one potassium channel activators has been prepared, and their *in vitro* relaxant activities in isolated rat portal vein and guinea pig tracheal spirals as well as their oral antihypertensive effect in spontaneously hypertensive rats have been evaluated. The group 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 antiarrhythmic 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 mechanism³ 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 compounds⁴ 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 Levromakalim, 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 companies⁶ (Chart I shows some). The benzopyran nucleus itself has also been modified, and series of thienopyranes,⁷ pyranopyridines,⁸ thienopyrans,⁹ tetrahydroquinolines and tetrahydronaphthalenes,¹⁰ benzoxepines,¹¹ 1,4-benzoxazines,¹² 1,3-benzoxazines,¹³ and indans¹⁴ 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 group¹⁵ 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

Chart I^a



^a Potassium channel openers under development.

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}

Chemistry

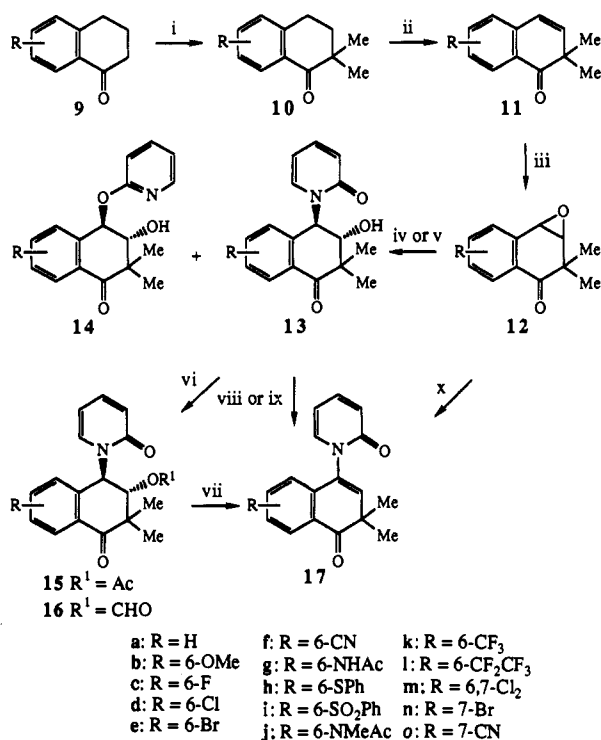
The synthesis of the present compounds involves opening the new 3,4-epoxy derivatives 12, which are obtained following the route outlined in Scheme I. The requisite 1-tetralones 9 are either commercially available (R = H, 6-OMe) or can be obtained using published procedures.¹⁶

Alkylation of 9 (NaH, MeI, C₆H₆) 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.

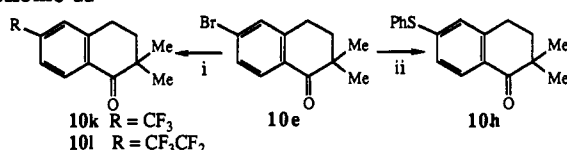
Bromination of compounds 10 with NBS/(PhCO)₂O₂/CCl₄ followed by immediate basic elimination gave olefins 11 (Table I). For nonhydrolyzable substituents at position 6, KOH in EtOH was used as the eliminating agent, whereas for groups susceptible to nucleophile attack, DBU proved to be the reagent of choice. 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 (i) NaH, IMe, PhH, reflux; (ii) (1) NBS, CCl₄, 60 °C; (2) KOH, EtOH, 45 °C or DBU, 85 °C; (iii) MCPBA, CH₂Cl₂; (iv) method A: 2-pyridone, pyridine, EtOH, reflux; (v) Method B: 2-[(trimethylsilyl)oxy]pyridine, FNBU₄, THF; (vi) Ac₂O (or HCHO), pyridine; (vii) method C: DBU, PhMe, reflux; (viii) method D: NaOH-SiO₂, dioxane, reflux; (ix) For R = CN: CuCN, NMP, reflux; (x) method E: 2-[(trimethylsilyl)oxy]pyridine, FNBU₄, THF, reflux.

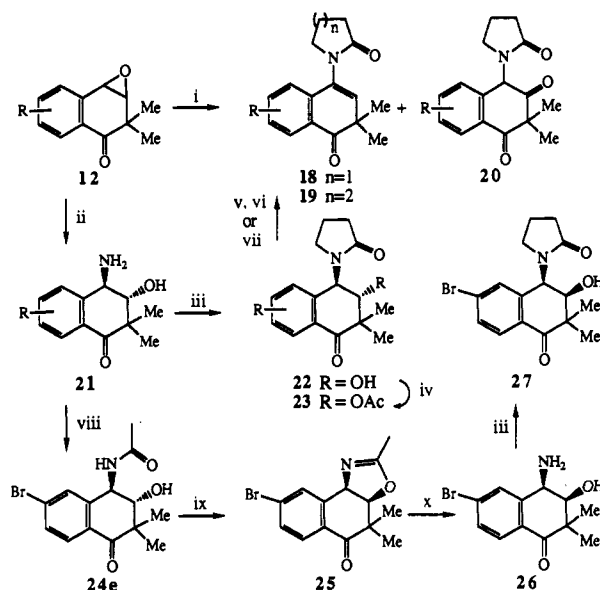
Scheme II^a

^a(i) CF₃CO₂Na (or CF₃CF₂CO₂Na), CuI, NMP, reflux; (ii) PhSH, K₂CO₃, NMP, 160 °C.

In all cases treatment of olefins 11 with MCPBA/CH₂Cl₂ 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 ethanol¹⁷ (method A) or via its *O*-silyl derivative¹⁸ (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 toluene¹⁹ (method C), from the 3-hydroxy derivatives 13 (NaOH, SiO₂, 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 NMP²⁰ 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) NH₃, EtOH, reflux; (iii) (1) ClCO(CH₂)₃Cl, NEt₃, CHCl₃; (2) K₂CO₃, KI, acetone, reflux; (iv) Ac₂O, pyridine; (v) DBU, PhMe, reflux; (vi) NaOH-SiO₂, dioxane, reflux; (vii) CuCN, NMP, reflux; (viii) ClCOCH₃, NEt₃, CHCl₃; (ix) DAST, CH₂Cl₂; (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 (PPh₃, PdAc₂, TEA)²¹ afforded 17p, which was transformed to the 6-ethynyl derivative 17q upon deprotection with K₂CO₃. This, in turn, was partially hydrogenated to the 6-ethenyl derivative 17s (H₂, Lindlar cat., quinoline, EtOH) or completely reduced to the 6-ethyl compound 17r (H₂, 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 imide 17u (MeONa, MeOH), the acid 17v (6 N HCl), the methyl ester 17w (MeOH, HClg), or the amide 17j (KOH, ^tBuOH) 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 (K₂CO₃, 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 ₂ Cl ₂	C ₁₃ H ₁₃ NO	C,H,N
10h	6-SPh	81	220–225 (0.5)		C ₁₈ H ₁₉ SO	C,H
10j	6-NMeAc	77	92–94	EtOAc	C ₁₅ H ₁₈ NO ₂ ·0.1H ₂ O	C,H,N
10k	6-CF ₃	59	28–30		C ₁₃ H ₁₃ F ₃ O	C,H
10l	6-CF ₂ CF ₃	63	130–135 (0.9)		C ₁₄ H ₁₃ F ₅ O	C,H
10m	6,7-Cl ₂	90	64–68	Et ₂ O	C ₁₂ H ₁₂ Cl ₂ O	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·0.75H ₂ O	C,H
11e	6-Br	74	49–52		C ₁₂ H ₁₁ BrO	C,H
11f	6-CN	68	104–105	CH ₂ Cl ₂	C ₁₃ H ₁₁ NO	C,H,N
11h	6-SPh	90	215–220 (0.5)		C ₁₈ H ₁₆ OS·0.25H ₂ O	C,H
11j	6-NMeAc	100	100–102	Et ₂ O	C ₁₈ H ₁₇ NO ₂	C,H,N
11k	6-CF ₃	100	65–70 (0.5)		C ₁₈ H ₁₁ F ₃ O	C,H
11l	6-CF ₂ CF ₃	84	105–110 (0.9)		C ₁₄ H ₁₁ F ₅ O	C,H
11m	6,7-Cl ₂	69	108	CH ₂ Cl ₂	C ₁₂ H ₁₀ Cl ₂ O	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 ·0.25H ₂ O	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 ₂ Cl ₂	C ₁₂ H ₁₁ ClO ₂ ·0.5H ₂ O	C,H
12e	6-Cl	55	85–86	CH ₂ Cl ₂	C ₁₂ H ₁₁ ClO ₂ ·0.5H ₂ O	C,H
12f	6-Br	71	105	EtOAc	C ₁₂ H ₁₁ BrO ₂	C,H
12g	6-CN	48	113–116	EtOAc	C ₁₈ H ₁₁ NO ₂ ·0.5H ₂ O	C,H,N
12i	6-SO ₂ Ph	50	56–58	Et ₂ O	C ₁₇ H ₁₆ O ₄ S	C,H
12j	6-NMeAc	71	129–131	EtOAc	C ₁₅ H ₁₇ NO ₃ ·0.25H ₂ O	C,H,N
12k	6-CF ₃	53	51	EtOAc	C ₁₃ H ₁₁ F ₃ O ₂	C,H
12l	6-CF ₂ CF ₃	77	71–72	EtOAc	C ₁₄ H ₁₁ F ₅ O ₂	C,H
12m	6,7-Cl ₂	66	91–93	CH ₂ Cl ₂	C ₁₂ H ₁₀ Cl ₂ O ₂ ·0.25H ₂ O	C,H
12n	7-Br	83	62–63	CH ₂ Cl 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 ₁₈ H ₁₄ N ₂ O ₂ ·0.25H ₂ O	C,H,N
21g	6-NMeAc	58	112	CH ₂ Cl ₂	C ₁₅ H ₂₀ N ₂ O ₃	C,H,N
21h	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 ₂ O ₄	C,H,N

^a Analyses for the elements indicated were within $\pm 0.4\%$ 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 cyanoacetamide 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·Me₂S, 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

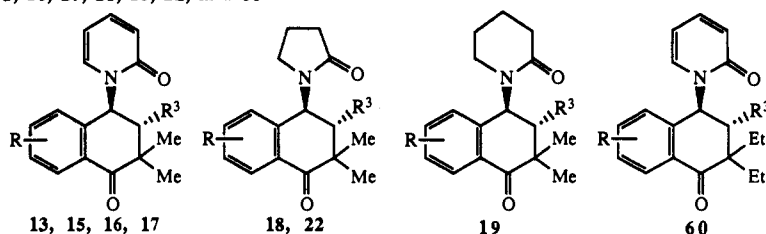
acetylated to give compound 49 and methylated to afford 50. Tetralone 17e was also reacted with methylmagnesium bromide to afford the 1-methyl-1-hydroxy derivative 51. The oxime derivatives 52–53, which consisted of mixtures of *E* and *Z* isomers, were obtained by reaction with the corresponding derivatized 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 °C²⁸ 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



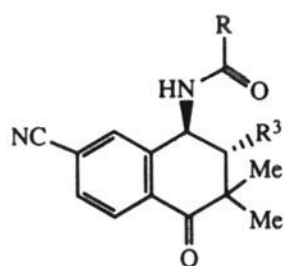
no.	R	R ³	mp, °C	recrystd solv	yield, % (method)	formula	anal. ^b	portal vein relaxation IC ₅₀ , ^c μM	max. fall in BP ^d ± SEM, mmHg	tracheal relaxation IC ₅₀ , ^e μM
13a	H	OH	263–265	M	13 (A)	C ₁₇ H ₁₇ NO ₃ ·0.6H ₂ O	C,H,N	NC (0) ^f	NS ^g	NT ^h
13b	6-OMe	OH	225	M	24 (A)	C ₁₈ H ₁₈ NO ₄	C,H,N	NC (0)	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 ₂ O ₃	C,H,N	14	84.0 ± 2.1	>10
13i	6-SO ₂ Ph	OH	186–190	EA	43 (B)	C ₂₃ H ₂₁ NO ₆ S·0.25H ₂ O	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 ₂ O ₄ ·H ₂ O	C,H,N	33	94.0 ± 10.0	>10
13k	6-CF ₃	OH	202–205	EA	44 (B)	C ₁₈ H ₁₆ F ₃ NO 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 ₂ NO ₃ ·0.25H ₂ O	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 ₁₈ 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 ₂ O ₄	C,H,N ⁱ	23	64.7 ± 32.6	2.0
16f	6-CN	OCHO	191–193	EA	55	C ₁₉ H ₁₈ N ₂ O ₄ ·0.25H ₂ O	C,H,N	36	42.0 ± 5.0	4.3
17b	6-OMe	Δ ^{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	Δ ^{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	Δ ^{3,4}	192.5	EA	71 (C)	C ₁₇ H ₁₄ ClNO ₂ ·0.25H ₂ O	C,H,N	1.4	53.7 ± 20.3	1.1
17e	6-Br	Δ ^{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	Δ ^{3,4}	187	EA	63	C ₁₈ H ₁₄ N ₂ O ₂	C,H,N	0.6	96.5 ± 17.3	0.5
17i	6-SO ₂ Ph	Δ ^{3,4}	83–90	EA	29 (E)	C ₂₂ H ₁₈ NO ₆ S·0.25H ₂ O	C,H,N	0.1	32.6 ± 7.7	0.5
17j	6-NMeAc	Δ ^{3,4}	160	EA	85 (C)	C ₂₀ H ₂₀ N ₂ O ₃	C,H,N	4.3	74.0 ± 11.1	3.1
17k	6-CF ₃	Δ ^{3,4}	130	EA	81 (D)	C ₁₈ H ₁₄ F ₃ NO ₂	C,H,N	0.3	103.0 ± 2.8	0.5
17l	6-CF ₂ CF ₃	Δ ^{3,4}	190	EA	71 (C)	C ₁₈ H ₁₄ F ₂ NO ₂	C,H,N	1 ^k	81.0 ± 13.7 ^j	1 ^k
17m	6,7-Cl ₂	Δ ^{3,4}	213	EA	75 (D)	C ₁₇ H ₁₃ Cl ₂ NO ₂ ·0.25H ₂ O	C,H,N	0.7	58.0 ± 4.2	0.1
17n	7-Br	Δ ^{3,4}	194	EA	71 (D)	C ₁₇ H ₁₄ BrNO ₂ ·0.25H ₂ O	C,H,N	2.7	37.0 ± 9.3	4.7
17o	7-CN	Δ ^{3,4}	214	E	38	C ₁₈ H ₁₄ N ₂ O ₂	C,H,N	NC (0)	41.0 ± 5.2	>10
17p	6-CCTMS	Δ ^{3,4}	84–94	EA	90	C ₂₂ H ₂₈ NO ₂ Si·0.5H ₂ O	C,H,N	0.5	91.5 ± 8.9	2.4
17q	6-CCH	Δ ^{3,4}	167–169	EA	74	C ₁₉ H ₁₆ NO ₂	C,H,N	1.0	94.0 ± 21.9	0.2
17r	6-Et	Δ ^{3,4}	51–52	DE	74	C ₁₈ H ₁₉ NO ₂ ·0.5H ₂ O	C,H,N	5.5	58.0 ± 13.4	5.1
17s	6-CH=CH ₂	Δ ^{3,4}	42–48	EA	74	C ₁₉ H ₁₇ NO ₂ ·0.5H ₂ O	C,H,N	1.5	30.6 ± 10.8	4.6
17t	6-OMe	Δ ^{3,4}	153–154	EA	45	C ₁₈ H ₁₇ NO ₃ ·0.25H ₂ O	C,H,N	3.3	56.5 ± 6.4	1.0
17u	6-C(NH)OMe	Δ ^{3,4}	198–200	EA	37	C ₁₈ H ₁₈ N ₂ O ₃ ·0.5H ₂ O	C,H,N	11	27.5 ± 13.8	3.1
17v	6-COOH	Δ ^{3,4}	293	EA	53	C ₁₈ H ₁₆ NO ₄ ·0.75H ₂ O	C,H,N	NC (0)	NS	>10
17w	6-COOMe	Δ ^{3,4}	188–189	EA	43	C ₁₉ H ₁₇ NO ₄ ·0.5H ₂ O	C,H,N	2.7	39.0 ± 16.0	8.5
17x	6-CONH ₂	Δ ^{3,4}	168	DE	52	C ₁₈ H ₁₆ N ₂ O ₃ ·0.5H ₂ O	C,H,N	NC (21)	NS	>10
17y	6-NHMe	Δ ^{3,4}	116–120	EA	56	C ₁₈ H ₁₈ N ₂ O ₃ ·0.25H ₂ O	C,H,N	52	NS	9.1
18a	H	Δ ^{3,4}	135–136	EA	41	C ₁₈ H ₁₇ NO ₂	C,H,N	NC (0)	NS	NT
18b	6-OMe	Δ ^{3,4}	100–101	E	32	C ₁₇ H ₁₆ NO ₃	C,H,N	NC (20)	NS	NT
18d	6-Cl	Δ ^{3,4}	161–162	EA	48	C ₁₆ H ₁₆ ClNO ₂ ·1H ₂ O	C,H,N	NC (0)	32.5 ± 5.4	>10
18e	6-Br	Δ ^{3,4}	96	EA	26	C ₁₈ H ₁₆ BrNO ₂	C,H,N	10	60.5 ± 7.5	7.3
18f	6-CN	Δ ^{3,4}	144	EA	83	C ₁₇ H ₁₆ N ₂ O ₂	C,H,N	0.8	103.0 ± 32.9	0.9
18j	6-NMeAc	Δ ^{3,4}	166–168	EA	83	C ₁₉ H ₂₂ N ₂ O ₃ ·0.5H ₂ O	C,H,N	17	23.0 ± 5.9	2.5
18n	7-Br	Δ ^{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	Δ ^{3,4}	95–100	EA	46	C ₁₇ H ₁₆ N ₂ O ₂ ·0.5H ₂ O	C,H,N	NC (0)	24.5 ± 8.5	NT
19e	6-Br	Δ ^{3,4}	50–52	EA	23	C ₁₇ H ₁₆ BrNO ₂	C,H,N	8.0	43.6 ± 13.3	3.5
22e	6-Br	OH	217	EA	63	C ₁₈ H ₁₆ BrNO ₃	C,H,N	NC (40)	39.0 ± 9.0	>10
22f	6-CN	OH	268	EA	63	C ₁₇ H ₁₆ N ₂ O ₃	C,H,N	NC (12)	23.0 ± 10.0	>10
60e	6-Br	Δ ^{3,4}	>300	EA	30	C ₁₉ H ₁₈ BrNO ₂ ·0.5H ₂ O	C,H,N	3.3	44.0 ± 8.8	8.0
60f	6-CN	Δ ^{3,4}	157	EA	58	C ₂₀ H ₁₈ N ₂ O ₂ ·0.7H ₂ O	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 isoproterenol. 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, CH₂, 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 ₂ O ₃	C, H, N	45	28.6 ± 9.9	8.7
28	2-pyridyl	OH	207–208	EA	82	C ₁₉ H ₁₇ N ₃ O ₃ ·0.25H ₂ O	C, H, N	23	71.7 ± 14.2	>10
29	3-pyridyl	OH	185–187	EA	70	C ₁₉ H ₁₇ N ₃ O ₃ ·1H ₂ O	C, H, N	2.8	50.0 ± 9.8	4.1
30	4-pyridyl	OH	223	EA	69	C ₁₉ H ₁₇ N ₃ O ₃	C, H, N	NC ^f (39)	NS ^g	>10
31	3-furyl	OH	220–224	EA	67	C ₁₈ H ₁₆ N ₂ O ₄	C, H, N	NC (24)	58.0 ± 17.5	NT ^h
32	phenyl	OH	230–234	MC	55	C ₂₀ H ₁₈ N ₂ O ₃ ·0.5H ₂ O	C, H, N	10	31.0 ± 11.9	1.8
33	4-MeOC ₆ H ₅	OH	205–208	MC	54	C ₂₁ H ₂₀ N ₂ O ₃ ·0.25H ₂ O	C, H, N	12	46.7 ± 8.6	12.2
34	2,4-Cl ₂ C ₆ H ₄	OH	100–104	EA	69	C ₂₀ H ₁₆ Cl ₂ N ₂ O ₃ ·0.25H ₂ O	C, H, N	NC(35)	NS	>10
35	3,4-Cl ₂ C ₆ H ₄	OH	225–228	EA	95	C ₂₀ H ₁₆ Cl ₂ N ₂ O ₃ ·0.5AcOEt	C, H, N	NC(67)	NS	>10
36	4-NO ₂ C ₆ H ₅	OH	249–250	EA	84	C ₂₀ H ₁₇ N ₃ O ₅	C, H, N	4.9	NS	7.9
37	2-pyridyl	Δ ^{3,4}	148	EA	67	C ₁₉ H ₁₅ N ₃ O ₂	C, H, N	9	22.5 ± 0.5	3.1

^{a-h} See corresponding footnotes of Table II.

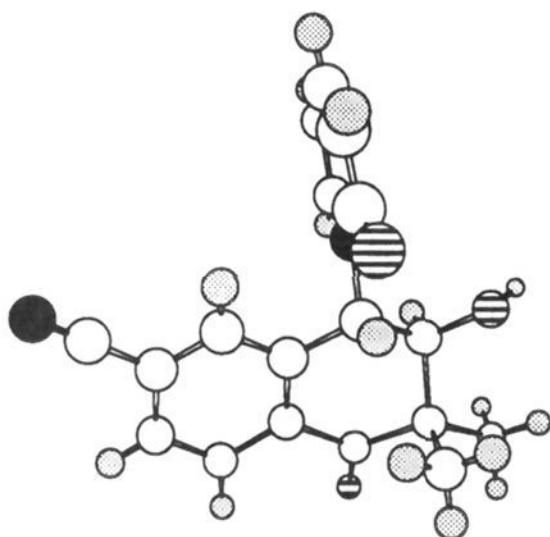


Figure 1. X-ray crystal structure of compound 13f. White circles indicate carbon atoms, dotted circles hydrogen atoms, striped circles oxygen atoms, and black circles nitrogen atoms.

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 H₄. 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 IC₅₀ values are plotted against the sigma value (σ_p)³⁰ of the corresponding phenyl ring substituents, a rough

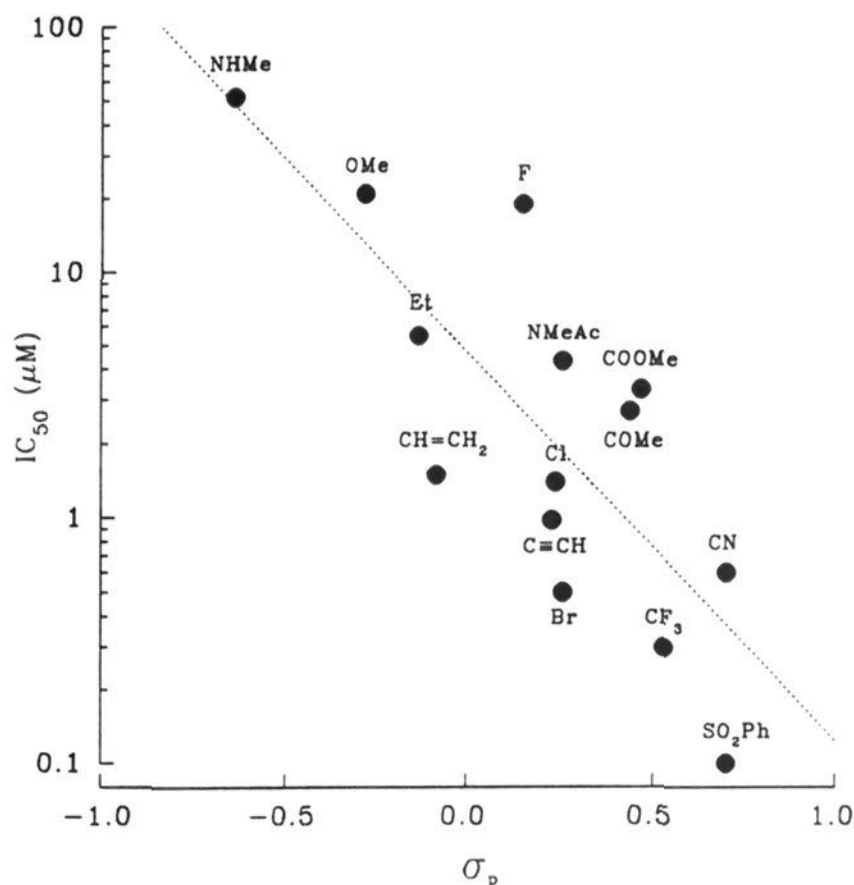


Figure 2. Variations of IC₅₀ in micromolar (logarithmic scale) against σ_p of substituents at 6-position of compounds 17. Regression parameters: $y = 14.1 - 29.3x$ ($r = 0.77$).

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 ₂ O ₃ ·0.25H ₂ O	C,H,N	25	43.0 ± 16.0	5.5
38e		Br	OH	249-252	EA	37	C ₂₀ H ₁₈ BrNO ₃ ·0.25H ₂ O	C,H,N ^h	3.1	24.0 ± 5.6	>10
38f		CN	OH	199-202	EA	33	C ₂₁ H ₁₈ N ₂ O ₃ ·0.75H ₂ O	C,H,N	0.5	76.0 ± 11.4	1.1
39		CN	Δ ^{3,4}	160-162	EA	28	C ₂₁ H ₁₈ N ₂ O ₂ ·0.25H ₂ O	C,H,N	0.6	34.0 ± 13.0	1.3
40		CN	OH	207-209	EA	40	C ₁₈ H ₁₆ N ₄ O ₂ ·0.25H ₂ O	C,H,N	NC (19)	NS ⁱ	3.5
41		Br	OH	231	EA	13	C ₁₈ H ₁₇ BrN ₄ O ₂ ·0.5H ₂ O·EtOH	C,H,N	NC (8)	27.6 ± 8.1	>10
42		Br	OH	241	EA	16	C ₁₈ H ₁₆ BrN ₃ O ₂ S·1.25H ₂ O	C,H,N	NC (26)	30.5 ± 13.7	NT
43		CN	OH	181	EA	4	C ₁₈ H ₁₂ NO ₄ ·2.25H ₂ O	C,H,N	NC (9)	50.0 ± 16.0	>10
44e		Br	OH	247-250	M	20	C ₁₈ H ₁₆ BrN ₂ O ₄ ·0.25H ₂ O	C,H,N	0.8	46.5 ± 0.3	4.4
44f		CN	OH	250-252	M	65	C ₁₇ H ₁₆ N ₃ O ₄	C,H,N	8.8	116.0 ± 5.9	2.1
45		CN	OH	159	EA	66	C ₁₈ H ₁₇ N ₃ O ₄ ·0.75H ₂ O	C,H,N	2.8	112.0 ± 1.0	0.6
46		CN	OH	156-157	EA	76	C ₂₀ H ₁₈ N ₃ O ₄ ·0.25H ₂ O	C,H,N	14	20.5 ± 0.5	3.9
47		CN	Δ ^{3,4}	120-123	EA	95	C ₁₇ H ₁₃ N ₃ O 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, CF₃, CF₂CF₃, or SO₂Ph 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 ₁₈ BrNO ₂	C,H,N	NC (38) ^g	NS ^h	>10
50	194	EA	64	C ₁₈ 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 ·0.25H ₂ O	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 ₃ O ₂ ·2H ₂ O	C,H,N	25	32.4 ± 8.1	>10
54	158	EA	93	C ₁₈ H ₁₇ N ₃ O ₂ ·1H ₂ O	C,H,N	8.0	83.0 ± 10.2	>10

^{a-c} 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 described²⁷ 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

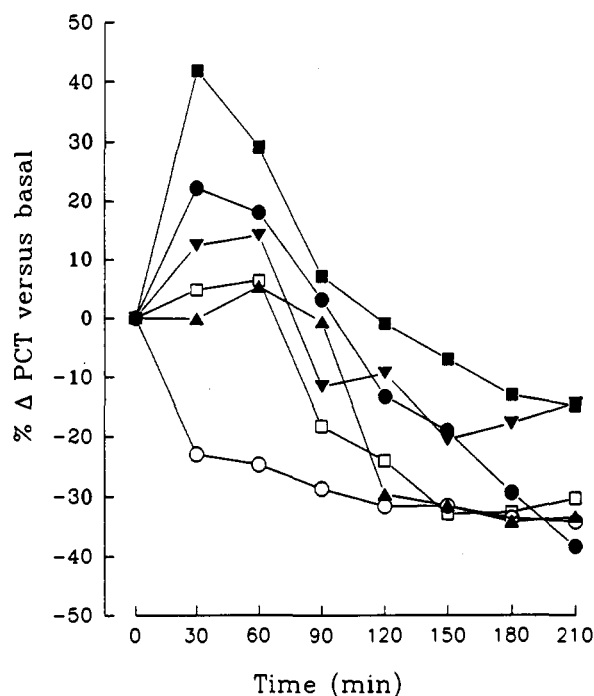


Figure 3. Percentage of increase of preconvulsive time (PCT) in an histamine induced bronchospasm after oral administration of vehicle (O), Levromakalim (□), 17e (▲), 17f (●), 17k (▼), and 17l (■) at a dose of 1 mg/kg. Each data point represents the mean value derived from eight experiments.

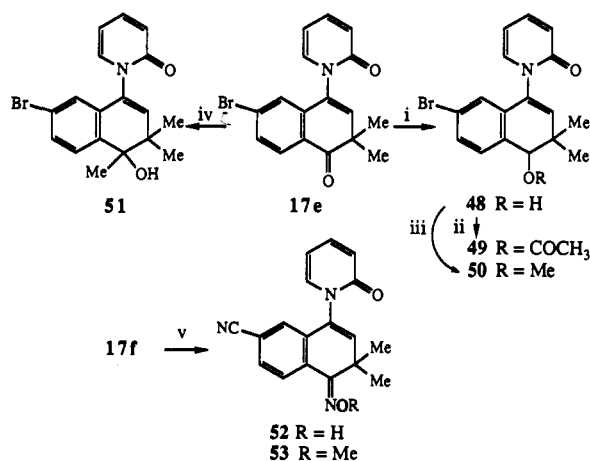
Table VI. ED₃₀ of Selected Compounds

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		

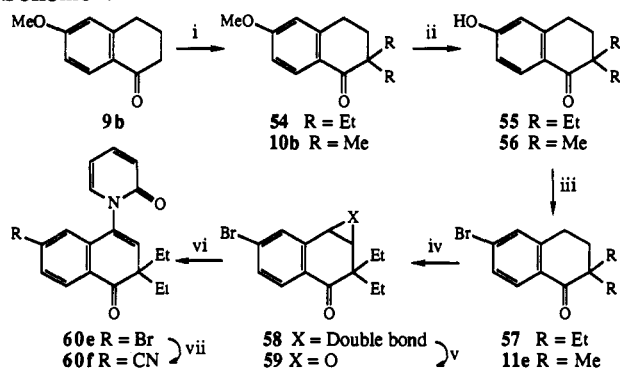
^a Dose required to decrease systolic blood pressure by 30 mmHg.

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 Levromakalim 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 ED₃₀ 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) NaBH₄, EtOH/THF; (ii) Ac₂O, pyridine; (iii) IMe, NaH, THF; (iv) MeMgI, THF; (v) NH₂OR·HCl, pyridine, MeOH, reflux.

Scheme V^a

^a (i) NaH, RI, PhH, reflux; (ii) 48% HBr, reflux; (iii) Br₂PPh₃, 200 °C; (iv) (1) NBS, CCl₄, 60 °C; (2) KOH, EtOH; (v) MCPBA, CH₂Cl₂; (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 ¹³C (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 Et₂O and washed with H₂O and 10% Na₂CO₃ solution. The organic phase was dried over MgSO₄, and the solvent was evaporated. The residue was purified by flash chromatography (hexane–CH₂Cl₂) to afford compound 10e as an oil (44.0 g, 80%): bp 155–160 °C (0.5 mmHg); ¹H NMR (80 MHz, CDCl₃) δ (TMS) 7.90 (d, *J* = 9 Hz, 1H, Ar), 7.39 (m, 2H, Ar), 2.96 (t, *J* = 6.5 Hz, 2H, CH₂Ar), 1.96 (t, *J* = 6.5 Hz, 2H, CH₂), 1.20 (s, 6H, 2 CH₃). Anal. (C₁₂H₁₃BrO) 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 K₂CO₃ (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 H₂O–Et₂O (1:1, 80 mL) mixture, and the aqueous phase was extracted with Et₂O. The combined organic phases were washed with 5% NaOH solution and with H₂O and dried over MgSO₄. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH₂Cl₂) to afford compound 10h as an oil (1.66 g, 81%): bp 220–225 °C (0.5 mmHg); ¹H NMR (80 MHz, CDCl₃) 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, CH₂Ar), 1.93 (t, *J* = 6.5 Hz, 2H, CH₂), 1.19 (s, 6H, 2 CH₃). Anal. (C₁₈H₁₈OS) 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 H₂O (600 mL) and Et₂O (600 mL). The layers were separated, and the aqueous phase was extracted with Et₂O. The combined organic phases were washed with H₂O and dried over MgSO₄. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH₂Cl₂) 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, CDCl₃) δ (TMS) 8.14 (d, *J* = 8.6 Hz, 1H, Ar), 7.53 (m, 2H, Ar), 3.05 (t, *J* = 6.4 Hz, 2H, CH₂Ar), 2.01 (t, *J* = 6.4 Hz, 2H, CH₂), 1.23 (s, 6H, 2 CH₃). Anal. (C₁₃H₁₃F₃O) C, H.

6-Bromo-2,2-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 CCl₄ (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 Et₂O, washed with H₂O and 5% Na₂CO₃ solution, and dried over MgSO₄. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH₂Cl₂) 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, CDCl₃) 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 CH₃). Anal. (C₁₂H₁₁BrO) 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 CCl₄ (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 Et₂O, washed with H₂O and 5% Na₂CO₃ solution, and dried over MgSO₄. The solvent was removed, and the residue was purified by flash chromatography (hexane–CH₂Cl₂) to afford 11f as a white solid, which was recrystallized from CH₂Cl₂ (1.92 g, 68%): mp 104–105 °C; ¹H NMR (80 MHz, CDCl₃) 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 CH₃). Anal. (C₁₃H₁₁NO) 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

CH₂Cl₂ (270 mL) was added 50% *m*-chloroperbenzoic acid (51.9 g, 0.17 mol) dissolved in CH₂Cl₂ (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% Na₂S₂O₅ and saturated NaHCO₃ solutions and dried over MgSO₄. 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, CDCl₃) 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, CH₃), 1.13 (s, 3H, CH₃). Anal. (C₁₂H₁₁BrO₂) 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, CDCl₃) δ (TMS) 7.96 (m, 1H, Ar), 7.54 (m, 3H, Ar), 7.2–6.2 (m, 4H, Ar + CHN), 4.05 (s, H₂O + OH), 3.95 (d, *J* = 8 Hz, 1H, CHOH), 1.38 (s, 3H, CH₃), 1.25 (s, 3H, CH₃). Anal. (C₁₇H₁₆BrNO₃) 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, CDCl₃) 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, CH₃), 1.25 (s, 3H, CH₃). Anal. (C₁₇H₁₆BrNO₃) 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-[(trimethylsilyloxy)pyridine (0.62 g, 3.7 mmol). The mixture was cooled to 0 °C, and Bu₄NF·3H₂O (0.88 g, 2.8 mmol) was added. After being stirred for 5 days at room temperature, the mixture was poured into H₂O, and the aqueous phase was extracted with EtOAc. The solution was dried over MgSO₄, and the solvent was removed to afford a residue that was treated with CH₂Cl₂. 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), Ac₂O (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 CH₂Cl₂ and washed with saturated NaHCO₃ solution and H₂O. The organic phase was dried over MgSO₄, 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, CD₃OD) 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, CH₃CO), 1.33 (s, 3H, CH₃), 1.26 (s, 3H, CH₃). Anal. (C₁₈H₁₈BrNO₄) 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 H₂O and dried over MgSO₄. 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, CDCl₃) 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, CH₃), 1.38 (s, 3H, CH₃). Anal. (C₁₇H₁₄BrNO₂) 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-[(trimethylsilyloxy)pyridine (35.0 g, 150 mmol). The mixture was cooled to 0 °C, and Bu₄NF·3H₂O (24.0 g, 75 mmol) was added. After being stirred for one night at reflux, the mixture was poured into H₂O and the aqueous phase was extracted with EtOAc. The solution was dried over MgSO₄, 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 H₂O and dried over MgSO₄. 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, CDCl₃) 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, CH₃), 1.40 (s, 3H, CH₃). Anal. (C₁₈H₁₄N₂O₂) 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 NEt₃ (6.5 mL) was added, under an argon atmosphere, PPh₃ (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 NaHCO₃ solution and CH₂Cl₂, the phases were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried over MgSO₄, 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. (C₂₂H₂₃NO₂Si·0.5H₂O) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-ethylnaphthalen-1-one (17q). A mixture of 17p (0.68 g, 1.9 mmol), K₂CO₃ (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 NaHCO₃ solution and CH₂Cl₂. The two phases were separated, and the aqueous phase was extracted with CH₂Cl₂. The combined organic phases were dried over MgSO₄, 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. (C₁₈H₁₈NO₂) 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. (C₁₈H₁₈NO₂·0.5H₂O) C, H, N.

1,2-Dihydro-4-(1,2-dihydro-2-oxo-1-pyridyl)-2,2-dimethyl-6-ethylnaphthalen-1-one (17s). A mixture of 17q (0.20 g, 0.69 mmol), 5% Pd on CaCO₃ (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. (C₁₈H₁₇NO₂·0.5H₂O) 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 Et₂O and filtered. The solid was washed with EtOAc, and the combined organic phases were washed with H₂O and dried over MgSO₄. 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. (C₁₆H₁₇NO₃·0.25H₂O) 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 H₂O (5 mL) and extracted with EtOAc. The solution was dried over MgSO₄, 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. (C₁₉H₁₉N₂O₅·0.5H₂O) 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, H₂O (5 mL) was added, and the mixture was extracted with CH₂Cl₂. The organic phase was extracted with 1 N NaOH, and the basic aqueous phase was acidified and extracted with CH₂Cl₂. The solution was dried over MgSO₄, 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. (C₁₆H₁₅NO₄·0.75H₂O) 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 H₂O (5 mL) was added to the residue. The mixture was extracted with CHCl₃, and the solution was dried over MgSO₄. 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. (C₁₈H₁₇NO₄·0.5H₂O) 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, H₂O (5 mL) was added to the residue, and the mixture was extracted with EtOAc. The organic phase was dried over MgSO₄ and concentrated to give 17x as a white solid, which was recrystallized from ether (0.14 g, 52%): mp 168 °C. Anal. (C₁₈H₁₈N₂O₃·0.5H₂O) 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 MgSO₄, 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. (C₁₈H₁₈N₂O₂·0.25H₂O) 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 H₂O (100 mL) and extracted with EtOAc. The organic phase was washed with H₂O and dried over MgSO₄. 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, CDCl₃) 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, CH₂N), 2.58 (m, 2H, CH₂CO), 2.31 (m, 2H, CH₂), 1.35 (s, 6H, 2 CH₃). Anal. (C₁₈H₁₆BrNO₂) 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, CDCl₃) δ (TMS) 8.23 (m, 1H, Ar), 7.94 (m, 2H, Ar), 5.29 (s, 1H, CHN), 3.52 (m, 2H, CH₂N), 2.6–1.9 (m, 4H, 2 CH₂), 1.35 (s, 3H, CH₃), 1.29 (s, 3H, CH₃). Anal. (C₁₈H₁₆BrNO₃) 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 NH₃ (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 Et₂O. The aqueous phase was basified with 1 N NaOH and extracted with Et₂O. The organic phase was dried over MgSO₄, 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, CDCl₃) 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, NH₂ + OH), 1.37 (s, 3H, CH₃), 1.13 (s, 3H, CH₃). Anal. (C₁₂H₁₄BrNO₂) 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 NEt₃ (0.43 mL, 3 mmol) in CHCl₃ (40 mL) was added 4-chlorobutyl chloride (0.432 g, 3 mmol), and the mixture was stirred for 1 h at room temperature. The organic phase was washed with H₂O and dried over MgSO₄. The solvent was removed and the residue purified by flash chromatography (hexane–EtOAc) to yield *trans*-6-bromo-4-[(4-chlorobutyl)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, CD₃OD) 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, CH₂Cl), 3.65 (d, *J* = 9.9 Hz, 1H, CHO), 2.58 (m, 4H, CH₂CO + OH + NH), 2.21 (m, 2H, CH₂), 1.33 (s, 3H, CH₃), 1.16 (s, 3H, CH₃). Anal. (C₁₈H₁₈BrClNO₃) C, H, N.

A mixture of the previous product (1.10 g, 2.8 mmol), K₂CO₃ (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 H₂O and extracted with CHCl₃. The organic phase was dried over MgSO₄, 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, CD₃OD) 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, H₂O + OH), 3.92 (d, *J* = 10.3 Hz, 1H, CHO), 3.46 (t, *J* = 7.6 Hz, 2H, CH₂N), 2.62 (m, 2H, CH₂CO), 2.17 (m, 2H, CH₂), 1.33 (s, 3H, CH₃), 1.16 (s, 3H, CH₃). Anal. (C₁₈H₁₈BrNO₃) 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 NEt₃ (0.12 mL, 0.9 mmol) in CHCl₃ (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 H₂O and dried over MgSO₄. 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, CDCl₃) 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, CH₃), 2.0 (br, s, 1H, OH), 1.36 (s, 3H, CH₃), 1.17 (s, 3H, CH₃). Anal. (C₁₅H₁₆N₂O₃) 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 CH₂Cl₂ (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, CDCl₃) 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, CH₃), 1.40 (s, 3H, CH₃), 1.18 (s, 3H, CH₃). Anal. (C₁₄H₁₄BrNO₂) 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 Et₂O. The aqueous phase was basified with 2 N NaOH and extracted with EtOAc. The solution was dried over MgSO₄, and the solvent was removed to give 26 as a white solid (1.4 g, 58%): mp 198 °C; ¹H NMR (80 MHz, CDCl₃) 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, CH₃), 1.18 (s, 3H, CH₃). Anal. (C₁₂H₁₄BrNO₂) 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 NaHCO₃ solution and H₂O and dried over MgSO₄. 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; ¹H NMR (80 MHz, CDCl₃) 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, CH₃), 1.25 (s, 3H, CH₃). Anal. (C₁₉H₁₇N₃O₃·0.25H₂O) C, H, N.

trans-4-(2,3-Dihydro-1-oxo-1H-isindol-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), K₂CO₃ (1.16 g, 8.4 mmol), and KI (0.233 g, 1.4 mmol) in CH₃CN (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 H₂O and 0.1 N Na₂S₂O₃, and dried over MgSO₄. 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; ¹H NMR (80 MHz, CDCl₃) 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, CH₂), 1.42 (s, 3H, CH₃), 1.26 (s, 3H, CH₃). Anal. (C₂₁H₁₈N₂O₃·0.75H₂O) 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; ¹H NMR (80 MHz, CDCl₃) 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, CH₃), 1.36 (s, 3H, CH₃), 1.19 (s, 3H, CH₃). Anal. (C₁₈H₁₈N₄O₂·0.25H₂O) 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 H₂O (100 mL) and extracted with EtOAc. The organic phase was washed with H₂O and dried over MgSO₄. 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; ¹H NMR (80 MHz, CDCl₃) 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, CH₃), 1.19 (s, 3H, CH₃). Anal. (C₁₈H₁₈BrN₃O₂S·1.25H₂O) 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·Me₂S (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 CHCl₃ and H₂O, and the aqueous phase was extracted with CHCl₃. The combined organic extracts were dried over MgSO₄, 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; ¹H NMR (80 MHz, CDCl₃) 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, CHO), 2.70 (m, 5H, 2 CH₂ + OH), 1.39 (s, 3H, CH₃), 1.27 (s, 3H, CH₃). Anal. (C₁₈H₁₇NO₄·2.25H₂O) 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 CH₂Cl₂. The resulting suspension was filtered to give 44f as a white solid, which was recrystallized from MeOH (0.50 g, 66%): mp 250–252 °C; ¹H NMR (80 MHz, CDCl₃-CD₃OD) 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, CHO), 3.68 (s, 2H, OH + NH), 1.36 (s, 3H, CH₃), 1.25 (s, 3H, CH₃). Anal. (C₁₇H₁₆N₃O₄) 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), K₂CO₃ (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 CHCl₃ and H₂O. The aqueous phase was extracted with CHCl₃, and the combined organic extracts were dried over MgSO₄. 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; ¹H NMR (80 MHz, CDCl₃) 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, CHO), 3.68 (s, 3H, CH₃), 2.0 (br s, 1H, OH), 1.42 (s, 3H, CH₃), 1.28 (s, 3H, CH₃). Anal. (C₁₈H₁₇N₃O₄·0.75H₂O) 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, NaBH₄ (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 MgSO₄ 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; ¹H NMR (80 MHz, CDCl₃) 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_{ax}-OH), 4.23 (s, 0.5H, CH_{ax}-OH), 3.52 (br s, 1H, OH), 1.29 (s, 1.5H, 0.5 CH₃), 1.17 (s, 1.5H, 0.5 CH₃), 1.04 (s, 1.5H, 0.5 CH₃), 0.95 (s, 1.5H, 0.5 CH₃). Anal. (C₁₇H₁₆BrNO₂) 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 Et₂O and washed with saturated NaHCO₃ solution and H₂O. The organic phase was dried over MgSO₄, 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; ¹H NMR (80 MHz, CD₃OD) 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, CH₃), 3.38 (s, 0.26 × 3H, CH₃), 1.23 (s, 3H, CH₃), 1.10 (s, 3H, CH₃). Anal. (C₁₈H₁₆BrNO₂·0.25H₂O) 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 Et₂O (1 mL) was added dropwise, under an argon atmosphere, a solution of IMe (0.09 mL, 1.4 mmol) in Et₂O (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 H₂O and the mixture acidified with 1 N H₂SO₄ solution. The phases

were separated, and the aqueous phase was extracted with Et₂O. The combined organic extracts were dried over MgSO₄, 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, CD₃OD) 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 (brs, 1H, OH), 1.7–1.0 (m, 9H, 3 CH₃). Anal. (C₁₈H₁₈BrNO₂) 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), MeONH₂·HCl (0.034 g, 0.41 mmol), pyridine (0.07 mL), and MeOH (1 mL) was stirred at reflux for 18 h. After additional MeONH₂·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 CHCl₃ and H₂O, and the aqueous phase was extracted with CHCl₃. The combined organic extracts were dried over MgSO₄, 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, CDCl₃) 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 OCH₃), 3.98 (s, 1.5H, 0.5 OCH₃), 1.64 (s, 1.5H, 0.5 CH₃), 1.59 (s, 1.5H, 0.5 CH₃), 1.44 (s, 1.5H, 0.5 CH₃), 1.26 (s, 1.5H, 0.5 CH₃). Anal. (C₁₉H₁₇N₃O₂·H₂O) 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 H₂O and extracted with Et₂O. The organic phase was extracted with 1 N NaOH. The aqueous phase was acidified with 1 N HCl and extracted with Et₂O. 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, CDCl₃) 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, CH₂Ar), 1.99 (t, *J* = 6.3 Hz, 2H, CH₂), 1.62 (m, 5H, 2 CH₂CH₃ + OH), 0.84 (t, *J* = 7.3 Hz, 6H, 2 CH₃).

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. (C₁₂H₁₄O₂·0.1H₂O) 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 H₂O and EtOAc, and the layers were separated. The aqueous phase was extracted with EtOAc, and the combined organic phases were dried over MgSO₄. 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, CDCl₃) δ (TMS) 7.89 (d, *J* = 8.9 Hz, 1H, Ar), 7.37 (m, 2H, Ar), 2.94 (t, *J* = 6.4 Hz, 2H, CH₂Ar), 2.00 (t, *J* = 6.4 Hz, 2H, CH₂), 1.61 (m, 4H, 2 CH₂CH₃), 0.84 (t, *J* = 7.5 Hz, 6H, 2 CH₃).

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: C₁₈H₁₈N₂O₃; *M* = 308.34; monoclinic; *P*₂/*n* (*C*_{2h}, 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 × 10⁶ pm³; *Z* = 4; ρ_x = 1.3513 g·cm⁻³; μ(Cu Kα) = 7.22 cm⁻¹; no. of reflections with *I* ≥ 3σ(*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 (Leticia) containing a physiological saline solution continuously bubbled with 5% CO₂, 95% O₂ 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 NaHCO₃, 4.7 mM KCl, 2.5 mM CaCl₂, 1.2 mM MgCl₂, 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 (IC₅₀) 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 sphygmomanometer (Leticia 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 ED₅₀ (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 (Leticia) containing Krebs-Henseleit solution at 37 °C, pH 7.4, continuously bubbled with carbogen (95% O₂ and 5% CO₂). 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 (EC₅₀) 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.

Acknowledgment. This work was done with support of the Plan de Fomento de la Investigación en la Industria Farmacéutica, from the Ministerio de Industria y Energía (Exp. 656/91). We thank M. Carmen Torres, Concepción González, Consol Ferreri, Guadalupe Martínez, Ana Ester Sanhuja, Olga González, and Teresa Gamero for their excellent technical assistance. We wish to extend our thanks to Jordi Belloc for the measurement of mass spectra and to Dr. C. K. Prout, Chemical Crystallography Laboratory, Oxford for providing us with X-ray data.

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-benzothioopyran-3-ols and their Sulphoxide and Sulphone Derivatives-Cromakalim Analogues. *J. Chem. Soc., Perkin Trans. 1* 1990, 3187-3191.
- (8) Burrell, G.; Cassidy, F.; Evans, J. M.; Lightowler, D.; Stemp, G. Variation in the Aromatic Ring of Cromakalim: Antihypertensive Activity of Pyranopyridines and 6-Alkyl-2H-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.; Bartrolí, 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.; Bartrolí, 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-NHCOCH₃: Allinger, N. L.; Jones, E. S. Synthesis of Some Functionally Substituted Benzocycanonones. *J. Org. Chem.* 1962, 27, 70-76. (b) R = 6-Cl: Hamilton, R. W. The antiarrhythmic and Antiinflammatory 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-Cl₂: 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) Burrell, 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-Heterocycloxy-2H-1-benzopyran Potassium Channel Activators. *J. Med. Chem.* 1990, 33, 2759-2767.
- (28) Wiley, G. A.; Hershkovitz, 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.