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Synthesis and Vasorelaxant Activity of 2-Fluoromethylbenzopyran Potassium Channel Openers

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Abstract—The synthesis and vasorelaxant activity of 2-fluoromethylbenzopyran potassium channel openers are described. These (2-fluoromethyl) derivatives displayed smooth muscle relaxant activities comparable to or more potent than the corresponding 2-methyl analogues.

Introduction

Potassium channel openers are recently discovered and novel class of compounds. Their pharmacological action involves the relaxation of smooth muscle by the opening of potassium channels, suggesting a number of therapeutic targets for this class of compounds such as hypertension, angina pectoris, coronary heart disease, asthma, urinary incontinence, and alopecia.[1] Potassium channel openers consist of a group of compounds with a diverse range of chemical structures such as cromakalim (**1**), pinacidil (**2**), and RP49356 (**3**) (Figure 1), whose synthetic efforts have been extensively made.[2] Cromakalim (**1**) is the prototype of the benzopyran potassium channel openers.[1] Recently, numerous benzopyran potassium channel openers have appeared. These include emakalim (**4**), bimakalim (**5**), and Ro 31-6930 (**6**).[1] These benzopyrans have a 2,2-dimethyl group in common, but little is known about the 2-fluoromethyl analogues. Introduction of fluorine, the most electronegative element known, into bioactive organic compounds can lead to significant and sometimes beneficial effects on the bioactivity, possibly due to its peculiar electronic, hydrophobic, and steric effects. With this in mind, we decided to introduce fluorine into the 2-methyl groups of the benzopyrans cromakalim (**1**), emakalim (**4**), bimakalim (**5**), and Ro 31-6930 (**6**), and to evaluate the effect of such transformation on their activity.

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Compounds selected were the 2,2-bis(fluoromethyl) derivatives (**9–14**, and **17**)[3] and 2,2-bis(trifluoromethyl) derivatives (**22**). The nitro, trifluoromethyl, and pentafluoroethyl groups at C-6 were also used in place of the cyano functional group, because such substitutions seemed to confer greater potency and tissue selectivity.[2e,4,5] Recently, the 2,2-bis(trifluoromethyl) derivative of cromakalim (**1**) has been prepared by a sophisticated but laborious process.[6] Here we report the synthesis and biological activity of new potassium channel openers, the 2-fluoromethylbenzopyrans.[3]

Chemistry

The synthesis and physical properties of 2-fluoromethylbenzopyrans are shown in Schemes 1–3, and Tables 1 and 2, respectively. 6-Cyanobenzopyran (**7a**) and 6-nitrobenzopyran (**7b**) were obtained by a procedure similar to that previously reported.[5f] 6-Perfluoroalkylbenzopyrans (**7c** and **7d**) were prepared from the 6-nitro derivative **7b** through the 6-iodo derivative **7e** by the standard method.[7] The benzopyrans **7** were treated with *m*-chloroperbenzoic acid (*m*-CPBA) to obtain the epoxides **8**. The epoxides **8** were converted to the mixture of *trans*-4-(cyclic amido)-3,4-dihydro-2*H*-1-benzopyran-3-ols (**9** and **11**) and 4-(cyclic amido)benzopyrans (**10** and **12**) by treatment with cyclic amide and a base (NaH or KO-*t*-Bu) (Method A) (Scheme 1). The epoxides **8** were also heated with 2-hydroxypyridine in pyridine to give the *trans*-4-(1,2-dihydro-2-oxo-1-pyr-

idyl)-3,4-dihydro-2*H*-1-benzopyran-3-ols **13** as main products. Dehydration of the 3,4-dihydrobenzopyran-3-ol derivatives **9**, **11**, and **13** produced the corresponding benzopyrans **10**, **12**, and **14** by treatment with methanesulfonyl chloride and triethylamine, respectively, followed by treatment with sodium hydride (Method B), or with sodium hydroxide-carrier in dioxane (Method C).

The synthesis of the 2-(2-fluoromethylbenzopyran-4-yl)pyridine *N*-oxide derivatives **17** and **22** is shown in

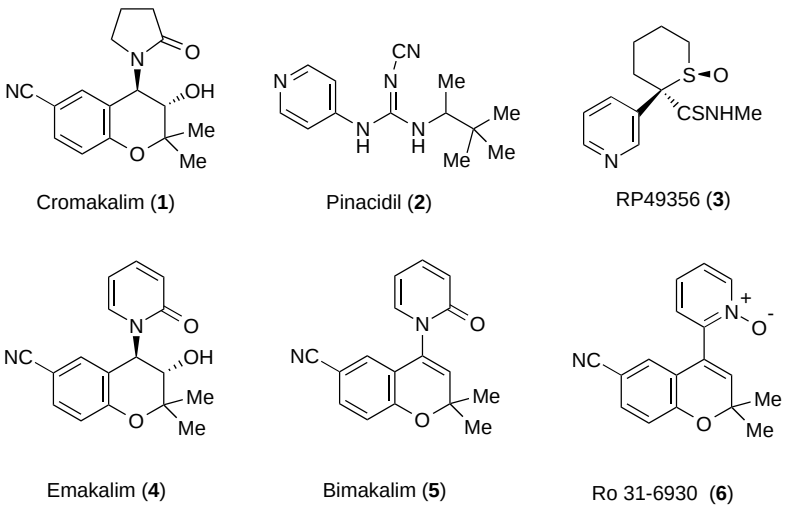
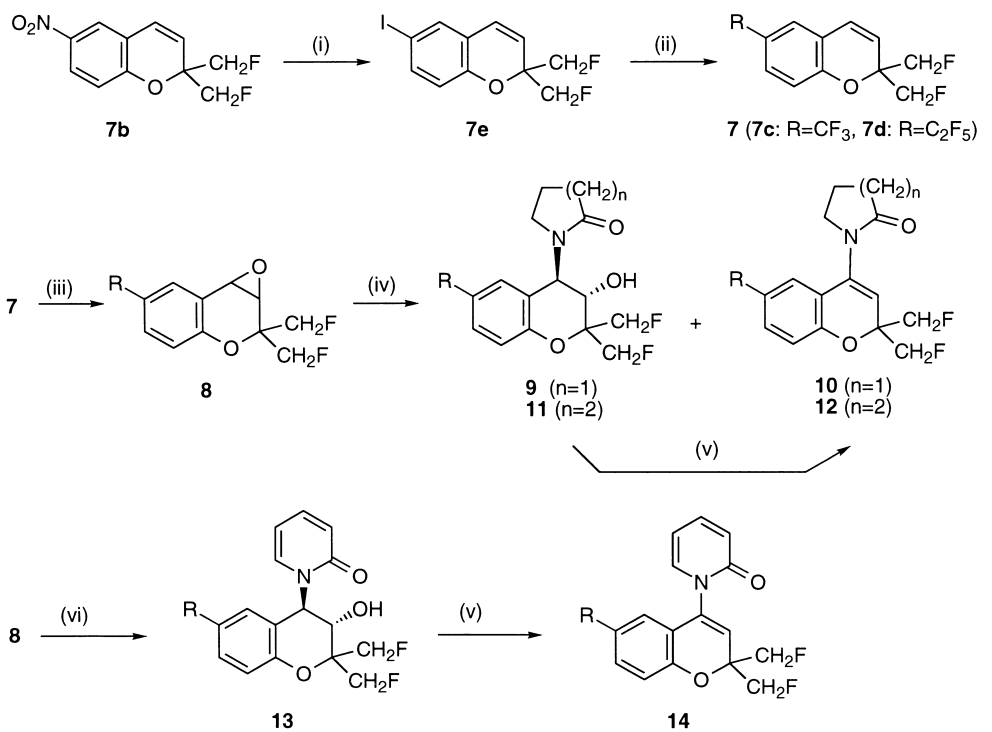
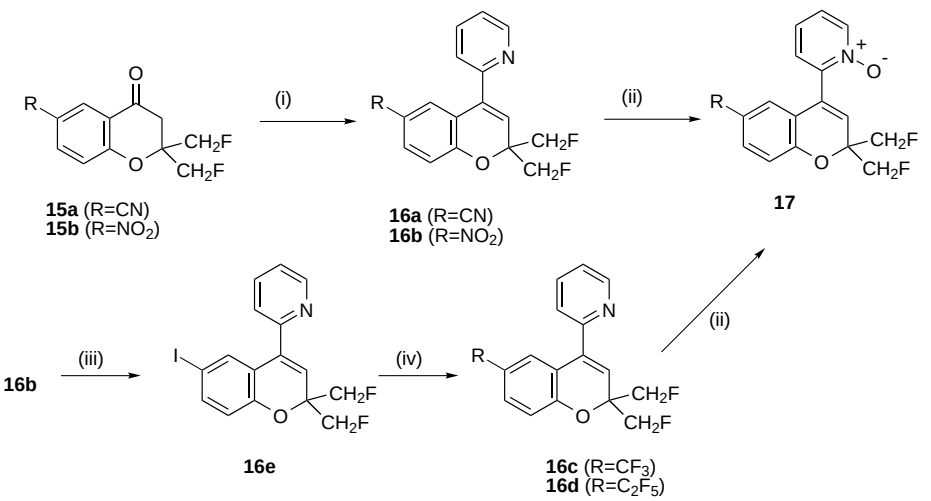


Figure 1.

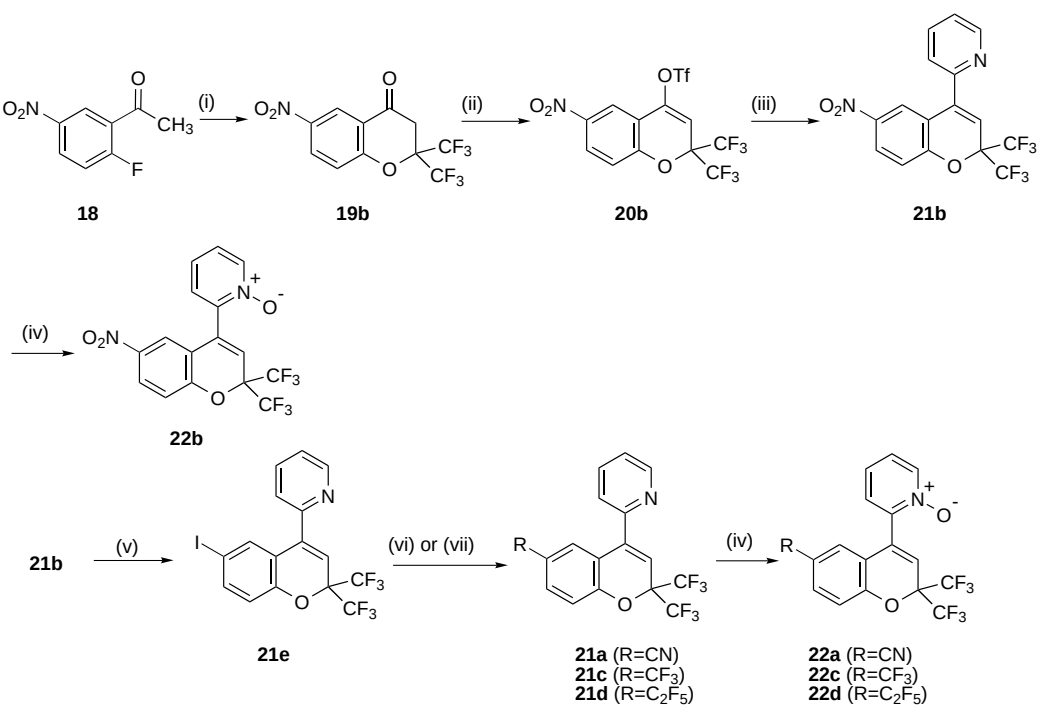


Scheme 1. (i) (a) $SnCl_2$, EtOH (b) $NaNO_2$, aq. H_2SO_4 (c) KI, CH_2Cl_2 (62% from **7b**) (ii) CF_3COOK or C_2F_5COOK, CuI, DMF, toluene (R = CF_3 82%, R = C_2F_5 75%) (iii) *m*-CPBA, CH_2Cl_2 (62–84%) (iv) 2-oxopyrrolidine or 2-oxopiperidine, NaH, DMSO (Method A) or KO-*t*-Bu, THF (Method B) (v) (a) MsCl, NEt_3, THF (b) NaH, THF (Method C) or NaOH-carrier, dioxane (Method D) (vi) 2-hydroxypyridine, pyridine, EtOH

Schemes 2 and 3. The known benzopyran-4-one **15b**[5f] was converted to the triflates by treatment with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 4-dimethylaminopyridine (DMAP), and the resulting triflates were allowed to react with 2-trimethylstannylpyridine in the presence of $Pd_2(dba)_3(CHCl_3)$ as the catalyst, to produce 6-nitro-4-(2-pyridyl)benzopyran **16b**.[8] The 6-cyano analogue **16a** was prepared from the



Scheme 2. (i) (a) Tf_2O, DMAP, CH_2Cl_2 (R = CN 39%, R = NO_2 83%) (b) 2-trimethylstannylpyridine, $Pd_2(dba)_3(CHCl_3)$, PPh_3, LiCl, THF (R = CN 83%, R = NO_2 79%) (ii) *m*-CPBA, CH_2Cl_2 (iii) (a) $SnCl_2$, EtOH (b) $NaNO_2$, conc. H_2SO_4, KI, CH_2Cl_2 (63% from **16b**) (iv) CF_3COOK or C_2F_5COOK, CuI, toluene, DMF (R = CF_3 82%, R = C_2F_5 70%).



Scheme 3. (i) $(CF_3)_2CO{\cdot}3H_2O$, pyrrolidine, benzene (21%) (ii) Tf_2O, DMAP, CH_2Cl_2 (97%) (iii)  , $Pd(PPh_3)_4$, THF (79%) (iv) *m*-CPBA, CH_2Cl_2 (v) (a) $SnCl_2$, EtOH (b) $NaNO_2$, conc. H_2SO_4, (c) KI, CH_2Cl_2 (71%) (vi) CuCN, DMF (86%) (vii) CF_3COOK or C_2F_5COOK, CuI, toluene, DMF (R = CF_3 63%, R = C_2F_5 73%).

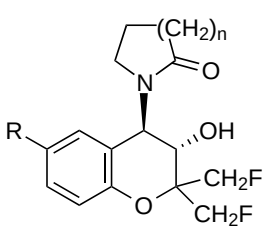
4-oxo derivative **15a**[9] in a similar way. The 6-perfluoroalkyl derivatives **16c** and **16d** were obtained from the 6-nitro compound **16b** by the same procedure as the synthesis of **7c** and **7d** (see Scheme 1). The 4-(2-pyridyl)benzopyrans **16** were then treated with *m*-CPBA to produce the *N*-oxides **17**.

For the synthesis of 2,2-bis(trifluoromethyl) benzopyran-4-one **19b**,[10] the cyclization reaction of 2′-fluoro-5′-nitroacetophenone (**18**) with hexafluoroacetone trihydrate in the presence of pyrrolidine was used, because the established synthesis routes[5f,11] that include the reaction of 2′-hydroxyacetophenones with carbonyl compounds in the presence of a base were problematic. The benzopyran-4-one **19b** was treated with Tf_2O in the presence of DMAP to obtain the triflate **20b**. Since the cross-coupling reaction of the triflate **20b** with 2-(trimethylstannyl)pyridine under Stille conditions was unsuccessful,[8] organozinc compounds which are more reactive than stannanes, were used.[12] Thus, the palladium-catalyzed coupling of **20b** with 2-pyridylzinc chloride produced the pyridine derivative **21b**. The low reactivity of the trifluoromethanesulfonyloxy group in **20b** presumably reflects an electronic effect due to the 2-trifluoromethyl groups.[6] The 6-cyanobenzopyran **21a** was prepared from the 6-nitrobenzopyran **21b** via 6-iodobenzopyran **21e**. The 6-perfluoroalkyl derivatives **21c** and **21d** were also prepared from 6-iodo derivative **21e** by a similar method to the above (see Scheme 3). The pyridines **21a–d** were readily converted into *N*-oxides **22a–d** by treatment with *m*-CPBA, without any detectable formation of products resulting from oxidation of the 3,4-double bond,[3,13] also suggesting the electronic and steric effects of the 2-trifluoromethyl groups.[6]

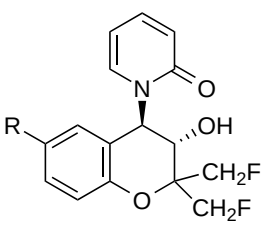
Results and Discussion

Vasorelaxant activity of the compounds were evaluated for the effects on 30 mM KCl responses by rat isolated

Table 1. Physical properties and vasorelaxant activity of 2,2-bis(fluoromethyl)-3,4-dihydrobenzopyran-3-ols



9 (n=1)
11 (n=2)



13

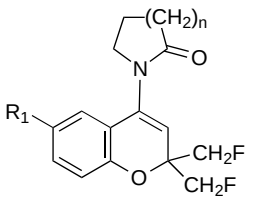
Compound	R	% yield[a]	mp,°C	Rat aorta		
				$_pEC_{50}$[b]	IA (%)[c]	n[d]
9a	CN	12	216–218	7.07 ± 0.08	78.0 ± 8.1	3
9b	NO_2	16	256–258	7.62 ± 0.10	72.7 ± 2.9	3
9c	CF_3	56	186–187	7.43	59.0	2
9d	C_2F_5	48	196–197	8.20 ± 0.02	77.6 ± 4.2	3
11a	CN	59	201–203	8.05 ± 0.03	74.9 ± 4.7	3
11b	NO_2	3	231–233	8.56 ± 0.01	63.3 ± 2.6	3
11c	CF_3	22	184–187	7.84	81.6	2
11d	C_2F_5	63	199–200	8.41 ± 0.10	65.6 ± 1.7	3
13a	CN	53	213–214	6.83 ± 0.06	78.7 ± 2.9	3
13b	NO_2	27	226–228	7.54 ± 0.10	74.5 ± 7.3	3
13c	CF_3	33	210–212	7.31	75.5	2
13d	C_2F_5	56	162–164	7.92 ± 0.14	82.8 ± 3.6	3
Cromakalim (**1**)				6.77 ± 0.03	74.1 ± 2.1	25
Pinacidil (**2**)				6.14 ± 0.03	91.9 ± 2.5	5
RP49356 (**3**)				6.28 ± 0.04	79.7 ± 2.2	6

[a]Satisfactory microanalysis was obtained for all crystalline compounds.
[b]Negative logarithm of the molar concentration required to relax rat aorta precontracted with 30 mM KCl by 50% of IA, with ± SEM. Details are described in the Experimental section.
[c]Intrinsic activity ± SEM (%).
[d]Number of determinations.

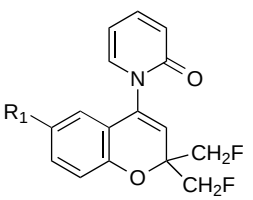
aorta, in comparison with cromakalim (**1**),[2b] pinacidil (**2**),[2a] RP49356 (**3**),[14] bimakalim (**5**),[11] and Ro 31-6930 (**6**)[2d,4] (Tables 1 and 2).

The 2-fluoromethylbenzopyran derivatives possessed the activities comparable to or more potent than the corresponding 2-methyl analogues. For the 3-hydroxy-2,2-bis(fluoromethyl) derivatives, cromakalim analogues **9a**, **11a**, and **13a** showed activity comparable to or more potent than cromakalim (**1**). Concerning the 4-substituents, the most favored one was 2-oxopiperidine group (**11**). Changing the 6-cyano group to nitro, trifluoromethyl, and pentafluoroethyl groups increased the activity (Table 1). Compared to the 3-hydroxy derivatives, the dehydrated compounds **10**, **12**, and **14** exhibited somewhat different structure-activity relationships (SAR) (Table 2). Dehydration of **9** and **13**, to give **10** and **14**, respectively, increased their activities, while the same operation for **11**, to yield **12**, increased their activities slightly, except for the 6-trifluoromethyl compound **12c**. For the dehydrated form, the most attractive 4-substituent varied depending on the 6-substituent.

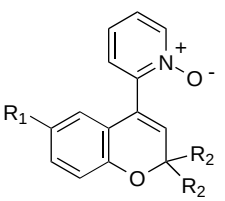
Table 2. Physical properties and vasorelaxant activities of benzopyrans



10 (n=1)
12 (n=2)



14



17 (R_2=CH_2F)
22 (R_2=CF_3)

Compound	R_1	Method	% yield[a]	mp, °C	Rat aorta		
					$_pEC_{50}$[b]	IA (%)[c]	n[d]
10a	CN	A	29	140–141	6.99 ± 0.07	74.4 ± 4.8	3
10b	NO_2	B	20	147–148	8.11 ± 0.09	74.3 ± 1.1	3
10c	CF_3	B	17	125–127	7.84	81.6	2
10d	C_2F_5	B	16	104–105	8.82 ± 0.06	68.6 ± 7.8	3
12a	CN	A	15	174–176	6.79 ± 0.05	68.7 ± 6.9	3
12b	NO_2	A	8	161–162	7.76 ± 0.05	69.7 ± 3.3	3
12c	CF_3	D	54	166–168	9.01	75.3	2
12d	C_2F_5	C	87	149–150	8.25 ± 0.08	72.0 ± 5.4	3
14a	CN	D	54	174–175	7.61 ± 0.07	75.7 ± 1.6	3
14b	NO_2	D	74	171–173	8.61 ± 0.01	64.9 ± 4.1	3
14c	CF_3	C	19	139–140	8.18	71.5	2
14d	C_2F_5	C	63	137–138	8.53 ± 0.04	69.2 ± 3.9	11
17a	CN		36	204–207	7.78 ± 0.10	71.1 ± 5.1	3
17b	NO_2		27	183–184	8.76 ± 0.10	66.3 ± 1.1	3
17c	CF_3		19	169–170	8.29	94.9	2
17d	C_2F_5		49	105–107	8.77 ± 0.16	68.2 ± 4.1	3
22a	CN		96	160–161	8.38	80.1	2
22b	NO_2		67	208–210	8.66 ± 0.02	50.3 ± 10.7	3
22c	CF_3		70	123–125	8.77	97.4	2
22d	C_2F_5		83	98–99	8.40 ± 0.22	64.4 ± 2.4	3
Cromakalim (**1**)					6.77 ± 0.03	74.1 ± 2.1	25
Pinacidil (**2**)					6.14 ± 0.03	91.9 ± 2.5	5
RP49356 (**3**)					6.28 ± 0.04	79.7 ± 2.2	6
Bimakalim (**5**)					7.52 ± 0.10	70.2 ± 4.3	4
Ro31-6930 (**6**)					7.61 ± 0.03	78.2 ± 8.6	3

[a]Satisfactory microanalysis was obtained for all crystalline compounds.
[b]Negative logarithm of the molar concentration required to relax rat aorta precontracted with 30 mM KCl by 50% of IA, with ± SEM. Details are described in the Experimental section.
[c]Intrinsic activity ± SEM (%).
[d]Number of determinations.

Thus, for 6-CN, NO_2, CF_3, and C_2F_5, the pyridone, pyridine, piperidone, and pyrrolidone, respectively, were the favored 4-substituents. The 6-nitro, trifluoromethyl, and pentafluoroethyl groups were superior to the 6-cyano group. The 2-fluoromethyl derivatives **17a** and **22a** had slightly increased activities compared to the prototype compound **6**. Thus, the pyridine *N*-oxide potassium channel openers exhibited excellent activities, especially in compounds containing 6-nitro, trifluoromethyl, and pentafluoroethyl groups. However, introduction of fluorine into the 2-methyl group only slightly increased activity.

In summary, introduction of fluorine into the 2-methyl group of benzopyran potassium channel openers did not change or slightly increased activity in vitro. On the other hand, in vivo evaluation revealed that these 2-fluoromethyl compounds showed slower onset and longer duration of antihypertensive activity and less tachycardia.[5f,15] These results suggest that the fluorine introduced into 2-position of the benzopyrans may lead to beneficial effects on the antihypertensive activity.

Experimental

Chemistry

Solvents and other reagents were reagent grade and were used without further purification unless otherwise noted. Tetrahydrofuran (THF) was dried over sodium and benzophenone. All melting points were determined with a Yanaco MP-3 melting point apparatus and are uncorrected. NMR spectra were obtained using a Hitachi R-24B 60 MHz, JEOL FX200 or JEOL FX270 spectrometer, and are expressed in ppm downfield from tetramethylsilane as the internal standard. EI mass spectra were recorded with a Shimadzu GCMS-QP1000 instrument. HR-FAB mass spectra were recorded with a VG Analytical VG11-250 instrument. Column chromatography was performed on silica gel C-200 (WAKO).

6-Amino-2,2-bis(fluoromethyl)-2*H*-1-benzopyran. To a solution of 2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran (**7b**; 4.67 g, 19.4 mmol) in 60 ml of EtOH, $SnCl_2$ (11.1 g, 58.5 mmol) was added at room temperature. The mixture was refluxed for 5 h. The resulting mixture was evaporated, basified with 2N NaOH and extracted with CH_2Cl_2. The organic layer was extracted with 2N HCl. The aqueous layer was basified with 2N NaOH and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to obtain 2.76 g of 6-amino-2,2-bis(fluoromethyl)-2*H*-1-benzopyran as an oil in 68% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.28 (brs, 2H), 3.81–5.04 (m, 4H, C$\underline{H}_2$F), 5.51 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.18–6.71 (m, 4H, 3(4)-H, arom. H). MS (EI) *m*/*z*: 211 (M^+).

2,2-Bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran (7e). To a stirred mixture of 6-amino-2,2-bis(fluoromethyl)-2*H*-1-benzopyran (2.67 g, 12.7 mmol) and c.H_2SO_4 (0.8 ml, 15.0 mmol) in 60 ml of H_2O, $NaNO_2$ (0.88 g, 12.8 mmol) dissolved in 10 ml of H_2O was added at 0 °C. After the mixture was stirred at 0 °C for 20 min, KI (2.54 g, 15.3 mmol) dissolved in 10 ml of H_2O and 80 ml of CH_2Cl_2 were added, and the mixture was stirred at room temperature for 2 h. The organic solution was washed with 2N NaOH, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using on silica gel (hexane:ethyl acetate = 1:1) to give 3.0 g of 2,2-bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran (**7e**) as an oil in 74% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.41 (d, $J = 46$ Hz, 2H, C$\underline{H}_2$F), 4.44 (d, $J = 46$ Hz, 2H, C$\underline{H}_2$F), 5.56 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.48 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.54 (d, $J = 8$ Hz, 1H, 8-H), 7.16–7.47 (m, 2H, 5,7-H). MS (EI) *m*/*z*: 322 (M^+).

2,2-Bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran (7c). A stirred solution of 2,2-bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran (**7e**; 2.45 g, 6.30 mmol), CF_3COOK (1.92 g, 12.6 mmol) and CuI (2.52 g, 13.2 mmol) in 30 ml of DMF and 15 ml of toluene was stirred at 160 °C for 7 h under N_2, while toluene was distilled off. The mixture was diluted with ether and filtered through celite. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:CH_2Cl_2 = 5:1) to give 1.34 g of 2,2-bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran (**7c**) as an oil in 67% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.48 (d, $J = 46$ Hz, 4H, C$\underline{H}_2$F), 5.62 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.55 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.85 (d, $J = 8$ Hz, 1H, 8-H), 7.08–7.40 (m, 2H, 5,7-H). MS (EI) *m*/*z*: 264 (M^+).

6-Pentafluoroethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran (7d). A stirred solution of 2,2-bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran (**7e**; 3.0 g, 9.32 mmol), C_2F_5COOK (3.76 g, 18.6 mmol) and CuI (3.78 g, 19.8 mol) in 40 ml of DMF and 15 ml of toluene was stirred at 160 °C for 3 h under N_2 while toluene was distilled off. The mixture was diluted with ether and filtered through celite. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:CH_2Cl_2 = 1:2) to give 2.2 g of 6-pentafluoroethyl-

2,2-bis(fluoromethyl)-2*H*-1-benzopyran (**7d**) as an oil in 75% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.50 (d, $J = 48$ Hz, 2H, $C\underline{H}_2F$), 4.52 (d, $J = 48$ Hz, 2H, $C\underline{H}_2F$), 5.66 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.59 (d, $J = 10$ Hz, 1H, 3(4)-H), 6.87 (d, $J = 8$ Hz, 2H, 8-H), 7.13–7.47 (m, 2H, 5,7-H). MS (EI) *m*/*z*: 314 (M^+).

2,2-Bis(fluoromethyl)-1a,7b-dihydro-2*H*-oxireno[*c*][1]benzopyran-6-carbonitrile (8a). To a stirred mixture of 6-cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran (3.0 g, 13.6 mmol) in 50 ml of CH_2Cl_2, *m*-CPBA (purity 70%, 5.7 g, 23.1 mmol) was added at 0 °C. The mixture was stirred at room temperature for 15 h. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:CH_2Cl_2 = 1:2) to give 2.7 g of 2,2-bis(fluoromethyl)-1a,7b-dihydro-2*H*-oxireno[*c*][1]benzopyran-6-carbonitrile (**8a**) in 84% yield.

Mp 94–95 °C (hexane-ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.82 (d, $J = 4$ Hz, 1H, 3(4)-H), 4.01 (d, $J = 4$ Hz, 1H, 3(4)-H), 4.64 (d, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 6.83 (d, $J = 8$ Hz, 1H, 8-H), 7.48 (dd, $J = 2$, 8 Hz, 1H, 7-H), 7.61 (d, $J = 2$ Hz, 1H, 5-H). Anal. calcd for $C_{12}H_9NO_2F_2$: C, 60.76; H, 3.82; N, 5.91; found: C, 60.85; H, 3.79; N, 5.89. MS (EI) *m*/*z*: 237 (M^+).

The epoxides (**8b**, **8c**, and **8d**) were prepared from the benzopyranes (**7b**, **7c**, and **7d**), respectively, in a similar manner to **8a**.

2,2-Bis(fluoromethyl)-1a,7b-dihydro-6-nitro-2*H*-oxireno[*c*][1]benzopyran (8b). Mp 123–125 °C (hexane-ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.82 (d, $J = 4$ Hz, 1H, 3(4)-H), 4.05 (d, $J = 4$ Hz, 1H, 3(4)-H), 4.60 (d, $J = 46$ Hz, 2H, $C\underline{H}_2F$), 4.65 (d, $J = 46$ Hz, 2H, $C\underline{H}_2F$), 6.86 (d, $J = 8$ Hz, 1H, 8-H), 7.94–8.27 (m, 2H, 5,7-H). Anal. calcd for $C_{11}H_9NO_4F_2$: C, 51.37; H, 3.53; N, 5.45; found: C, 51.60; H, 3.58; N, 5.38. MS (EI) *m*/*z*: 257 (M^+).

2,2-Bis(fluoromethyl)-1a,7b-dihydro-6-trifluoromethyl-2*H*-oxireno[*c*][1]benzopyran (8c). oil. ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.78 (d, $J = 4$ Hz, 1H, 3(4)-H), 4.00 (d, $J = 4$ Hz, 1H, 3(4)-H), 4.18–5.10 (m, 4H, $C\underline{H}_2F$), 6.90 (d, $J = 8$ Hz, 1H, 8-H), 7.33–7.67 (m, 2H, 5,7-H). MS (EI) *m*/*z*: 280 (M^+).

2,2-Bis(fluoromethyl)-1a,7b-dihydro-6-pentafluoroethyl-2*H*-oxireno[*c*][1]benzopyran (8d). oil. ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.75 (d, $J = 5$ Hz, 1H, 3(4)-H), 3.96 (d, $J = 5$ Hz, 1H, 3(4)-H), 4.29–5.24 (m, 4H, $C\underline{H}_2F$), 6.81 (d, $J = 8$ Hz, 1H, 8-H), 7.24–7.43 (m, 2H, 5,7-H). MS (EI) *m*/*z*: 330 (M^+).

***trans*-2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (9a) and 2,2-bis(fluoromethyl)-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (10a) (Method A).** To a stirred solution of 2-pyrrolidinone (0.13 g, 1.88 mmol) and NaH (60% dispersion in mineral oil, 72 mg, 1.80 mmol) in 6 ml of DMSO, 2,2-bis(fluoromethyl)-1a,7b-dihydro-2*H*-oxireno[*c*][1]benzopyran-6-carbonitrile (**8a**; 0.4 g, 1.69 mmol) was added at 10 °C. The solution was stirred for 6 h at 10 °C. The mixture was diluted with ethyl acetate, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 64 mg of *trans*-2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (**9a**) which was the higher polarity component in 12% yield.

Mp 216–218 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.01–2.21 (m, 2H, $NCH_2C\underline{H}_2$), 2.50–2.64 (m, 2H, $NC\underline{H}_2CH_2$), 2.99–3.16 (m, 1H, $C\underline{H}_2CO$), 3.24–3.43 (m, 1H, $C\underline{H}_2CO$), 3.97 (d, $J = 7.1$ Hz, 1H, 4-H), 4.21 (dd, $J = 7.1$, 11.4 Hz, 1H, 3-H), 4.50–4.99 (m, 4H, $C\underline{H}_2F$), 5.40 (d, $J = 11.4$ Hz, 1H, O$\underline{H}$), 7.01 (d, $J = 8.6$ Hz, 1H, 8-H), 7.21 (d, $J = 2.3$ Hz, 1H, 5-H), 7.49 (dd, $J = 2.3$, 8.6 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{16}N_2O_3F_2$: C, 59.62; H, 5.00; N, 8.69; found: C, 59.37; H, 5.14; N, 8.58.

2,2-Bis(fluoromethyl)-4-(2-oxo-1-pyrrolidinyl)-2*H*-1-benzopyran-6-carbonitrile (150 mg) (**10a**) was then obtained as the lower polarity component in 18% yield.

Mp 140–141 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.85–2.75 (m, 4H, $NCH_2C\underline{H}_2$), 3.61 (t, $J = 6$ Hz, 2H, $C\underline{H}_2CO$), 4.52 (d, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 5.60 (s, 1H, 3-H), 6.88 (d, $J = 8$ Hz, 1H, 8-H), 7.19 (d, $J = 2$ Hz, 1H, 5-H), 7.38 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{14}N_2O_2F_2$: C, 63.15; H, 4.64; N, 9.21; found: C, 63.17; H, 4.75; N, 9.19. MS (EI) *m*/*z*: 304 (M^+).

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-nitro-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (9b) and 1-[2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (10b) (Method B).** To a stirred solution of 2,2-bis(fluoromethyl)-1a,7b-dihydro-6-nitro-2*H*-oxireno-[*c*][1]benzopyran (**8b**; 0.52 g, 2.02 mmol) and 2-pyrrolidinone (0.18 g, 2.11 mmol) in 10 ml of THF, KO*t*-Bu (0.28 g, 2.50 mmol) was added at 0 °C. The solution was stirred for 23 h at 0 °C. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2) to give 0.11 g of *trans*-1-[2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-nitro-2*H*-1-benzopyran-4-yl]-2-

pyrrolidinone (**9b**) which was the higher polarity component in 16% yield.

Mp 256–258 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$-DMSO-d_6, 60 MHz) δ: 1.90–2.70 (m, 4H, NCH_2CH_2), 2.90–3.70 (m, 2H, CH_2CO), 4.00–4.60 (m, (m, 1H, 3(4)-H), 4.77 (d, $J = 46$ Hz, 4H, CH_2F), 5.00–5.50 (m, 1H, 3(4)-H), 6.28 (d, $J = 8$ Hz, 1H, OH), 7.09 (d, $J = 8$ Hz, 1H, 8-H), 7.77 (d, $J = 2$ Hz, 1H, 5-H), 8.12 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{15}H_{16}N_2O_5F_2$: C, 52.63; H, 4.71; N, 8.18; found: C, 52.58; H, 4.66; N, 8.18.

0.10 g of 1-[2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (**10b**) was then obtained as the lower polarity component in 15% yield.

Mp 147–148 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 2.00–2.90 (m, 4H, NCH_2CH_2), 3.71 (t, $J = 6$ Hz, 2H, CH_2CO), 4.62 (d, $J = 46$ Hz, 4H, CH_2F), 5.72 (s, 1H, 3-H), 7.01 (d, $J = 8$ Hz, 1H, 8-H), 7.88 (d, $J = 2$ Hz, 1H, 5-H), 8.12 (dd, 1H, 7-H). Anal. calcd for $C_{15}H_{14}N_2O_4F_2$: C, 55.56; H, 4.35; N, 8.64; found: C, 55.62; H, 4.53; N, 8.68. MS (EI) *m*/*z*: 324 (M^+).

The compounds (**9c** and **10c**, **9d** and **10d**) were prepared in the manner of Method B.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (9c) and 1-[2,2-bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (10c). 9c**: Mp 186–187 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 2.12–2.14 (m, 2H, NCH_2CH_2), 2.56–2.64 (m, 2H, NCH_2CH_2), 3.06–3.25 (m, 1H, OH), 3.28–3.36 (m, 2H, CH_2CO), 4.23–4.29 (m, 1H, 3(4)-H), 4.63-4.91 (m, 4H, CH_2F), 5.47 (d, $J = 10.6$ Hz, 1H, 3(4)-H), 7.07 (d, $J = 8.9$ Hz, 1H, 8-H), 7.19 (d, $J = 2.0$ Hz, 1H, 5-H), 7.48 (dd, $J = 2.0$, 8.9 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{16}NO_3F_5$: C, 52.61; H, 4.42; N, 3.83; found: C, 52.54; H, 4.38; N, 3.81.

10c: mp 125–127 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 2.01–2.78 (m, 4H, NCH_2CH_2), 3.63 (t, $J = 6$ Hz, 2H, CH_2CO), 4.55 (d, $J = 46$ Hz, 4H, CH_2F), 5.65 (s, 1H, 3-H), 6.96 (d, $J = 8$ Hz, 1H, 8-H), 7.20 (d, $J = 2$ Hz, 1H, 5-H), 7.43 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{14}NO_2F_5$: C, 55.34; H, 4.06; N, 4.03; found: C, 55.56; H, 4.04; N, 4.08. MS (EI) *m*/*z*: 347 (M^+).

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (9d) and 1-[2,2-bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2-pyrrolidinone (10d). 9d**: mp 196–197 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.72–2.80 (m, 4H, NCH_2CH_2), 2.80–3.54 (m, 2H, CH_2CO), 4.00–4.36 (m, 1H, 3-H), 4.76 (d, $J = 48$ Hz, 4H, CH_2F), 4.77 (d, $J = 7$ Hz, 1H, OH), 5.47 (d, $J = 10$ Hz, 1H, 4-H), 7.07 (d, $J = 8$ Hz, 1H, 8-H), 7.15 (brs, 1H, 5-H), 7.49 (brd, $J = 8$ Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{16}NO_3F_7$: C, 49.17; H, 3.88; N, 3.37; found: C, 49.20; H, 3.91; N, 3.38.

10d: mp 104–105 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.90–2.80 (m, 4H, NCH_2CH_2), 3.61 (t, $J = 6$ Hz, 2H, CH_2CO), 4.58 (d, $J = 48$ Hz, 2H, CH_2F), 4.60 (d, $J = 48$ Hz, 2H, CH_2F), 5.67 (s, 1H, 3-H), 7.01 (d, $J = 8$ Hz, 1H, 8-H), 7.15 (d, $J = 2$ Hz, 1H, 5-H), 7.46 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{14}NO_2F_7$: C, 51.39; H, 3.55; N, 3.53; found: C, 51.44; H, 3.58; N, 3.51. MS (EI) *m*/*z*: 397 (M^+).

***trans*-2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-carbonitrile (11a).** To a stirred solution of 2,2-bis(fluoromethyl)-1a,7b-dihydro-2*H*-oxireno[*c*][1]benzopyran-6-carbonitrile (**8a**; 0.30 g, 1.27 mmol) and 2-piperidone (0.14 g, 1.41 mmol) in 10 ml of THF, KO-*t*-Bu (0.22 g, 1.96 mmol) was added at 0 °C. The solution was stirred for 8 h at 0 °C, and for an additional 16 h at room temperature. The mixture was diluted with ethyl acetate, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 0.25 g of *trans*-2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-carbonitrile (**11a**) in 59% yield.

Mp 201–203 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.66–2.00 (m, 4H, CH_2CH_2), 2.44–2.75 (m, 2H, NCH_2), 2.78–3.28 (m, 2H, CH_2CO), 4.12–4.42 (m, 2H, 3-H, OH), 4.49–4.92 (m, 4H, CH_2F), 6.01 (d, $J = 11.4$ Hz, 1H, 4-H), 7.01 (d, $J = 8.0$ Hz, 1H, 8-H), 7.25 (d, $J = 2.3$ Hz, 1H, 5-H), 7.45 (dd, $J = 2.3$, 8.0 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{18}N_2O_3F_2$: C, 60.71; H, 5.39; N, 8.33; found: C, 60.67; H, 5.71; N, 8.18.

The compounds (**11b**, **11c**, and **11d**) were prepared from the epoxides (**8b**, **8c**, and **8d**), respectively, in a similar manner to **11a**.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-nitro-2*H*-1-benzopyran-4-yl]-2-piperidinone (11b).** Mp 231–233 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.60–2.10 (m, 4H, CH_2CH_2), 2.30–2.70 (m, 2H, NCH_2), 2.80–3.20 (m, 2H, CH_2CO), 4.00–4.80 (m, 2H, 3-H, OH), 4.68 (d, $J = 46$ Hz, 4H, CH_2F), 5.95 (brs, 1H, 4-H), 6.97 (d, $J = 8$ Hz, 1H, 8-H), 7.78 (d, $J = 2$ Hz, 1H, 5-H), 8.02 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{18}N_2O_5F_2$: C, 53.93; H, 5.09; N, 7.86; found: C, 53.50; H, 5.20; N, 7.68.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (11c)**. Mp 184–187 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.58–2.11 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 2.33–2.71 (m, 2H, $NC\underline{H}_2$), 2.85–3.23 (m, 2H, $C\underline{H}_2CO$), 4.72 (d, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 4.76–4.94 (m, 1H, OH), 5.79–6.17 (m, 1H, 4-H), 6.98 (d, $J = 8$ Hz, 1H, 8-H), 7.12 (d, $J = 2$ Hz, 1H, 5-H), 7.39 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{18}NO_3F_5$: C, 53.83; H, 4.78; N, 3.69; found: C, 53.84; H, 4.77; N, 3.64.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (11d)**. mp 199–200 °C (hexane-ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.60–2.10 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 2.33–2.76 (m, 2H, $NC\underline{H}_2$), 2.76–3.40 (m, 2H, $C\underline{H}_2CO$), 3.99–4.34 (m, 1H, 3-H), 4.72 (brd, $J = 47$ Hz, 4H, $C\underline{H}_2F$), 4.83 (d, $J = 6$ Hz, 1H, OH), 5.99 (brd, $J = 10$ Hz, 1H, 4-H), 6.99 (d, $J = 8$ Hz, 1H, 8-H), 7.08 (brs, 1H, 5-H), 7.38 (brd, $J = 8$ Hz, 1H, 7-H). Anal. calcd for $C_{18}H_{18}NO_3F_7$: C, 50.36; H, 4.23; N, 3.26; found: C, 50.28; H, 4.48; N, 3.32.

2,2-Bis(fluoromethyl)-4-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-carbonitrile (12a). To a stirred solution of 2-piperidone (0.14 g, 1.40 mmol) and NaH (60% dispersion in mineral oil, 63 mg, 1.58 mmol) in 6 ml of DMSO, 2,2-bis-(fluoromethyl)-1a,7b-dihydro-2*H*-oxireno[*c*][1]benzopyran-6-carbonitrile (**8a**; 0.35 g, 1.48 mmol) was added at 10 °C. The solution was stirred for 6 h at 10 °C. The mixture was diluted with ethyl acetate, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 70 mg of 2,2-bis(fluoromethyl)-4-(2-oxo-1-piperidinyl)-2*H*-1-benzopyran-6-carbonitrile (**12a**) in 15% yield.

Mp 174–176 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.73–2.23 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 2.30–2.76 (m, 2H, $NC\underline{H}_2$), 3.25–3.74 (m, 2H, $C\underline{H}_2CO$), 4.76 (d, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 5.63 (s, 1H, 3-H), 6.89 (d, $J = 8$ Hz, 1H, 8-H), 7.11 (d, $J = 2$ Hz, 1H, 5-H), 7.41 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{16}N_2O_2F_2$: C, 64.15; H, 5.07; N, 8.80; found: C, 64.01; H, 5.27; N, 8.78. MS (EI) *m*/*z*: 318 (M^+).

The compound **12b** was prepared from the epoxide **8b**, respectively, in a similar manner to **12a**.

1-[2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-2-piperidinone (12b). mp 161–162 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.70–2.30 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 2.40–2.80 (m, 2H, $NC\underline{H}_2$), 3.40–3.70 (m, 2H, $C\underline{H}_2CO$), 4.64 (d, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 5.72 (s, 1H, 3-H), 6.98 (d, $J = 8$ Hz, 1H, 8-H), 7.77 (d, $J = 2$ Hz, 1H, 5-H), 8.08 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{16}N_2O_4F_2$: C, 56.81; H, 4.77; N, 8.28; found: C, 56.85; H, 4.74; N, 8.16. MS (EI) *m*/*z*: 338 (M^+).

1-[2,2-Bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (12c) (Method D). To a stirred solution of *trans*-1-[2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (**11c**; 0.12 g, 0.33 mmol) in 2 ml of dioxane, sodium hydroxide on support (0.12 g) was added at room temperature. The solution was refluxed for 1 h. The mixture was diluted with ethyl acetate, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 0.06 g of 1-[2,2-bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (**12c**) in 54% yield.

Mp 166–168 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.62–2.08 (m, 2H), 2.32–2.72 (m, 2H), 2.81–3.15 (m, 2H, $NC\underline{H}_2$), 3.30–3.61 (m, 2H, $C\underline{H}_2CO$), 4.54 (d, $J = 46$ Hz, 2H, $C\underline{H}_2F$), 4.70 (d, $J = 46$ Hz, 2H, $C\underline{H}_2F$), 5.63 (s, 1H, 3-H), 6.81–7.26 (m, 2H, 5,8-H), 7.40 (dd, $J = 2$, 8 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{16}NO_2F_5$: C, 56.51; H, 4.46; N, 3.88; found: C, 56.50; H, 4.44; N, 3.84. MS (EI) *m*/*z*: 361 (M^+).

1-[2,2-Bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (12d) (Method C). To a stirred solution of *trans*-1-[2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (**11d**; 0.23 g, 0.54 mmol) in 8 ml of THF, methanesulfonyl chloride (0.11 g, 0.96 mmol) and triethylamine (0.07 g, 0.69 mmol) were added at room temperature. The solution was stirred for 22 h. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The resulting residue was diluted with 4 ml of THF, to a stirred solution was added NaH (60% dispersion in mineral oil, 50 mg, 1.25 mmol) at 0 °C. The solution was stirred for 65 h at room temperature. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 0.12 g of 1-[2,2-bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2-piperidinone (**12d**) in 87% yield.

Mp 149–150 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 1.62–2.28 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 2.28–2.85 (m, 2H, $NC\underline{H}_2$), 3.29–3.75 (m, 2H, $C\underline{H}_2CO$), 4.63 (brd, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 5.69 (s, 1H, 3-H), 7.03 (d, $J = 9$ Hz, 1H, 8-H), 7.12 (d, $J = 2$ Hz, 1H, 5-H), 7.48 (dd, $J = 2$, 9 Hz, 1H, 7-H). Anal. calcd for $C_{18}H_{14}NO_2F_7$: C, 52.56; H, 3.92; N, 3.41; found: C, 52.37; H, 4.05; N, 3.41. MS (EI) *m*/*z*: 411 (M^+).

***trans*-2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1(2*H*)-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (13a)**. To a stirred solution of 2,2-bis(fluoromethyl)-1a,7b-dihydro-2*H*-oxireno[*c*][1]benzopyran-6-carbonitrile (**8a** ; 0.35 g, 1.48 mmol) and 2-hydroxypyridine (0.22 g, 2.31 mmol) in 3 ml of ethanol, pyridine (0.10 ml, 1.24 mmol) was added at room temperature. The solution was refluxed for 3 h, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 98:2) to give 0.26 g of *trans*-2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1(2*H*)-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (**13a**) in 37% yield.

Mp 213–214 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.21–4.40 (m, 1H, 3-H), 4.53–4.93 (m, 4H, C$\underline{H}_2$F), 5.63 (d, J = 5.1 Hz, 1H), 6.29 (dd, J = 5.7, 7.4 Hz, 1H), 6.46 (d, J = 9.7 Hz, 1H, 4-H), 6.61 (d, J = 8.6 Hz, 1H), 6.96 (d, J = 5.7 Hz, 1H), 7.02 (1H, brs, 5-H), 7.09 (d, J = 8.0 Hz, 1H, 8-H), 7.36–7.48 (m, 1H), 7.54 (brd, J = 8.0 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{14}N_2O_3F_2$: C, 61.45; H, 4.25; N, 8.43; found: C, 61.45; H, 4.47; N, 8.39.

The compounds (**13b**, **13c**, and **13d**) were prepared from the epoxides (**8b**, **8c**, and **8d**), respectively, in a similar manner to **13a**.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-nitro-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (13b)**. Mp 226–228 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$-DMSO-d_6, 60 MHz) δ: 3.20–3.80 (m, 1H), 4.10–5.60 (m, 1H), 4.73 (d, J = 46 Hz, 4H, C$\underline{H}_2$F), 6.10–6.80 (m, 3H), 7.12 (d, J = 8 Hz, 1H, 8-H), 7.30–7.90 (m, 3H, 5-H), 8.05 (dd, J = 2, 8 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{14}N_2O_5F_2$: C, 54.55; H, 4.01; N, 7.95; found: C, 54.53; H, 4.03; N, 7.93.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (13c)**. Mp 210–212 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 4.33 (brd, J = 9.2 Hz, 1H), 4.68–4.89 (m, 5H, C$\underline{H}_2$F,), 6.30 (t, J = 6.6 Hz, 1H), 6.49 (d, J = 9.6 Hz, 1H), 6.71 (d, J = 9.2 Hz, 1H), 6.95 (d, J = 6.6 Hz, 1H), 7.04 (brs, 1H, 5-H), 7.16 (d, J = 8.6 Hz, 1H, 5-H), 7.40–7.47 (m, 2H), 7.53 (brd, J = 8.6 Hz, 1H, 7-H). Anal. calcd for $C_{17}H_{14}NO_3F_5$: C, 54.41; H, 3.76; N, 3.73; found: C, 54.41; H, 3.66; N, 3.74.

***trans*-1-[2,2-Bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (13d)**. Mp 162–164 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.12–4.55 (m, 1H), 4.73 (d, J = 47 Hz, 2H, C$\underline{H}_2$F), 4.78 (d, J = 47 Hz, 2H, C$\underline{H}_2$F), 4.95–5.60 (m, 1H), 6.05–6.70 (m, 3H), 6.70–7.04 (m, 2H), 7.10–7.55 (m, 3H). Anal. calcd for $C_{18}H_{14}NO_3F_7$: C, 50.83; H, 3.32; N, 3.29; found: C, 50.82; H, 3.33; N, 3.32.

2,2-Bis(fluoromethyl)-4-(2-oxo-1(2*H*)-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (14a) (Method D). To a stirred solution of *trans*-2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-4-(2-oxo-1(2*H*)-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (**13a**; 0.13 g, 0.39 mmol) in 2 ml of dioxane, sodium hydroxide on support (0.13 g) was added at room temperature. The solution was refluxed for 45 min. The mixture was diluted with ethyl acetate, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 0.13 g of 2,2-bis(fluoromethyl)-4-(2-oxo-1(2*H*)-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (**14a**) in 54% yield.

Mp 174–175 °C (ethanol). ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 4.66 (m, J = 46 Hz, 4H, C$\underline{H}_2$F), 5.85 (s, 1H, 3-H), 6.29 (dt, J = 2, 6 Hz, 1H), 6.66 (d, J = 8 Hz, 1H), 6.98–7.07 (m, 2H), 7.41 (dd, J = 2, 6 Hz, 1H), 7.42–7.56 (m, 2H). Anal. calcd for $C_{17}H_{12}N_2O_2F_2$: C, 64.97; H, 3.85; N, 8.91; found: C, 64.81; H, 3.85; N, 8.80. MS (EI) m/z: 314 (M^+).

Compound **14b** was prepared from compound **13b** by Method D.

1-[2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-2-(1*H*)-pyridinone (14b). Mp 171–173 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.68 (d, J = 46 Hz, 4H, C$\underline{H}_2$F), 5.69 (s, 1H, 3-H), 6.30 (dt, J = 2, 6 Hz, 1H), 6.63 (d, J = 8 Hz, 1H), 7.02 (d, J = 8 Hz, 1H, 8-H), 7.08–7.70 (m, 3H), 8.10 (dd, J = 2, 8 Hz, 1H, 7-H). Anal. calcd for $C_{16}H_{12}N_2O_4F_2$: C, 57.49; H, 3.62; N, 8.38; found: C, 57.66; H, 3.62; N, 8.33. MS (EI) m/z: 334 (M^+).

1-[2,2-Bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (14d) (Method C). To a stirred solution of *trans*-1-[2,2-bis(fluoromethyl)-3,4-dihydro-3-hydroxy-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (**13d**; 0.15 g, 0.35 mmol) in 10 ml of THF, methanesulfonyl chloride (0.07 g, 0.61 mmol) and triethylamine (0.08 g, 0.79 mmol) were added at room temperature. The solution was stirred for 8 h. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. The resulting residue was diluted with 4 ml of THF, to a stirred solution was added NaH (60% dispersion in mineral oil, 60 mg, 1.50 mmol) at 0 °C. The solution was stirred for 66 h at room temperature. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography

of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 0.09 g of 1-[2,2-bis-(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (**14d**) in 63% yield.

Mp 137–138 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.69 (d, $J = 47$ Hz, 4H, C$\underline{H_2}$F), 5.84 (s, 1H, 3-H), 6.26 (dt, $J = 2$, 6 Hz, 1H), 6.65 (brd, $J = 9$ Hz, 1H), 6.82–7.05 (m, 1H), 7.13 (brs, 1H), 7.19–7.74 (m, 3H). Anal. calcd for $C_{18}H_{12}NO_2F_7$: C, 53.08; H, 2.97; N, 3.44; found: C, 53.17; H, 2.73; N, 3.43. MS (EI) *m*/*z*: 407 (M^+).

Compound **14c** was prepared from compound **13c** by Method C.

1-[2,2-Bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-2(1*H*)-pyridinone (14c). Mp 139–140 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.57 (d, $J = 46$ Hz, 4H, C$\underline{H_2}$F), 5.71 (s, 1H), 6.16 (dt, $J = 2$, 6 Hz, 1H), 6.51 (d, $J = 8$ Hz, 1H), 6.71–7.02 (m, 2H), 7.06–7.50 (m, 3H). Anal. calcd for $C_{17}H_{12}NO_2F_5$: C, 57.15; H, 3.39; N, 3.92; found: C, 57.19; H, 3.40; N, 3.86. MS (EI) *m*/*z*: 357 (M^+).

Trifluoromethanesulfonic acid 6-cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl ester. To a mixture of 2,2-bis(fluoromethyl)-2,3-dihydro-4-oxo-2*H*-1-benzopyran-6-carbonitrile (**15a**; 0.2 g, 0.84 mmol) and 4-dimethylaminopyridine (3.09 g, 25.3 mmol) in 12 ml of CH_2Cl_2, trifluoromethanesulfonic anhydride (0.35 ml, 2.13 mmol) was added dropwise with stirring at 0 °C. The mixture was stirred at 0 °C for 15 min and then stirred at room temperature for 1 h. The mixture was diluted with CH_2Cl_2, washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:CH_2Cl_2 = 1:1) to give 0.12 g of trifluoromethanesulfonic acid 6-cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl ester in 38% yield.

Mp 61–62 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.56 (d, $J = 46$ Hz, 2H, C$\underline{H_2}$F), 4.59 (d, $J = 46$ Hz, 2H, C$\underline{H_2}$F), 5.80 (1H, s, 3-H), 6.99 (d, $J = 8$ Hz, 1H, 8-H), 7.39–7.72 (m, 2H, 5,7-H). Anal. calcd for $C_{13}H_8NO_4SF_5$: C, 42.29; H, 2.18; N, 3.79; found: C, 42.35; H, 2.15; N, 3.73. MS (EI) *m*/*z*: 369 (M^+).

2,2-Bis(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (16a). A mixture of trifluoromethanesulfonic acid 6-cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl ester (120 mg, 0.33 mmol), 2-trimethylstannylpyridine (87 mg, 0.36 mmol), $Pd_2(dba)_3(CHCl_3)$ (25.4 mg, 0.02 mmol), Ph_3P (12.8 mg, 0.05 mmol) and LiCl (110 mg, 2.60 mmol) in 6 ml of THF was refluxed for 6.5 h. The mixture was diluted with ether and filtered through celite. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2) to give 80 mg of 2,2-bis(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (**16a**) in 83% yield.

Mp 94–95 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.51 (d, $J = 46$ Hz, 2H, C$\underline{H_2}$F), 4.58 (d, $J = 46$ Hz, 2H, C$\underline{H_2}$F), 5.93 (s, 1H, 3-H), 6.97 (d, $J = 8$ Hz, 1H, arom. H), 7.18–7.99 (m, 5H, arom. H), 8.52–8.83 (m, 1H, arom. H). Anal. calcd for $C_{17}H_{12}N_2OF_2$: C, 68.45; H, 4.06; N, 9.39; found: C, 68.51; H, 4.04; N, 9.47. MS (EI) *m*/*z*: 298 (M^+).

Compound **16b** was prepared from **15b** in a similar manner to **16a**.

Trifluoromethanesulfonic acid 2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl ester. oil. ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.54 (d, $J = 46$ Hz, 4H, C$\underline{H_2}$F), 5.74 (s, 1H, 3-H), 6.93 (d, $J = 9$ Hz, 1H, 8-H), 7.88–8.21 (m, 2H, 5,7-H). MS (EI) *m*/*z*: 389 (M^+).

2-[2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-pyridine (16b). Mp 105–106 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.60 (d, $J = 46$ Hz, 2H, C$\underline{H_2}$F), 4.62 (d, $J = 46$ Hz, 2H, C$\underline{H_2}$F), 5.98 (s, 1H, 3-H), 7.00 (d, $J = 8$ Hz, 1H, arom. H), 7.18–7.57 (m, 2H, arom. H), 7.75 (dd, $J = 2$, 8 Hz, 1H, arom. H), 8.07 (dd, $J = 2$, 8 Hz, 1H, arom. H), 8.27 (d, $J = 2$ Hz, 1H, arom. H), 8.60–8.83 (m, 1H, arom. H). Anal. calcd for $C_{16}H_{12}N_2O_3F_2$: C, 68.38; H, 3.80; N, 8.80; found: C, 60.44; H, 3.89; N, 8.66. MS (EI) *m*/*z*: 318 (M^+).

2,2-Bis(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-amine. To a solution of 2-[2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-pyridine (**16b**; 0.8 g, 2.52 mmol) in 10 ml of EtOH, $SnCl_2$ (1.7 g, 8.06 mmol) was added at room temperature. The mixture was refluxed for 3 h. The resulting mixture was evaporated, basified with 2N NaOH and extracted with CH_2Cl_2. The organic layer was extracted with 2N HCl. To the aqueous layer was basified with 2N NaOH and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated to obtain 0.64 g of 2,2-bis(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-amine as an oil in 88% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.44 (brs, 2H, NH_2), 3.95–5.20 (m, 4H, C$\underline{H_2}$F), 5.88 (s, 1H, 3-H), 6.48–6.89 (m, 3H, arom. H), 7.09–7.88 (m, 3H, arom. H), 8.56–8.75 (m, 1H, arom. H). MS (EI) *m*/*z*: 288 (M^+). HRMS (FAB) calcd for $C_{16}H_{15}N_2OF_2$: 289.1152 ($M^+ + 1$); found: 289.1192 ($M^+ + 1$).

2-[2,2-Bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran-4-yl]-pyridine (16e). To a stirred mixture of 2,2-bis-(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-amine (0.64 g, 2.22 mmol) and c.H_2SO_4 (0.14 ml, 2.62 mmol) in 10 ml of H_2O, $NaNO_2$ (0.16 g, 2.32 mmol) dissolved in 1.5 ml of H_2O was added at 0 °C. After the mixture was stirred at 0 °C for 30 min, KI (0.44 g, 2.65 mmol) dissolved in 1.5 ml of H_2O and 15 ml of CH_2Cl_2 were added and the mixture was stirred at room temperature for 1.5 h. The organic solution was washed with 2N NaOH, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:ethyl acetate = 5:1) to give 0.45 g of 2-[2,2-bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran-4-yl]-pyridine (**16e**) as an oil in 51% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.56 (m, 4H, C$\underline{H}_2$F), 5.86 (s, 1H, 3-H), 6.68 (d, $J = 8$ Hz, 1H, arom. H), 7.09–7.88 (m, 5H, arom. H), 8.55–8.72 (m, 1H, arom. H). MS (EI) *m/z*: 399 (M^+). HRMS (FAB) calcd for $C_{16}H_{13}NOF_2I$: 400.0010 ($M^+ + 1$); found: 400.0090 ($M^+ + 1$).

2-[2,2-Bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-pyridine (16c). A stirred solution of 2-[2,2-bis-(fluoromethyl)-6-iodo-2*H*-1-benzopyran-4-yl]-pyridine (**16e**; 1.40 g, 3.51 mmol), CF_3COOK (1.07 g, 7.02 mmol) and CuI (1.40 g, 7.35 mmol) in 20 ml of DMF and 10 ml of toluene was stirred at 160 °C for 6.5 h under N_2 while toluene was distilled off. The mixture was diluted with ether and filtered through celite. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:ethyl acetate = 5:1) to give 0.98 g of 2-[2,2-bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-pyridine (**16c**) in 82% yield.

Mp 89–90 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.63 (d, $J = 46$ Hz, 4H, C$\underline{H}_2$F), 5.96 (s, 1H, 3-H), 7.03 (d, $J = 8$ Hz, 1H, arom. H), 7.23–7.68 (m, 5H, arom. H), 8.60–8.83 (m, 1H, arom. H). Anal. calcd for $C_{17}H_{12}NOF_5$: C, 59.83; H, 3.54; N, 4.10; found: C, 59.78; H, 3.57; N, 4.04. MS (EI) *m/z*: 341 (M^+).

2-[6-Pentafluoroethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine (16d). A stirred solution of 2-[2,2-bis(fluoromethyl)-6-iodo-2*H*-1-benzopyran-4-yl]-pyridine (**16e**; 0.45 g, 1.13 mmol), C_2F_5COOK (0.46 g, 2.26 mmol) and CuI (0.45 g, 2.26 mmol) in 7 ml of DMF and 5 ml of toluene was stirred at 160 °C for 4 h under N_2 while toluene was distilled off. The mixture was diluted with ether and filtered through celite. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 99:1) to give 0.31 g of 2-[6-pentafluoroethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine (**16d**) as an oil in 70% yield.

^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.59 (d, $J = 46$ Hz, 4H, C$\underline{H}_2$F), 5.90 (s, 1H, 3-H), 6.98 (d, $J = 8$ Hz, 1H, arom. H), 7.08–7.82 (m, 5H, arom. H), 8.51–8.68 (m, 1H, arom. H). MS (EI) *m/z*: 391 (M^+). HRMS (FAB) calcd for $C_{18}H_{13}NOF_7$: 392.0885 ($M^+ + 1$); found: 392.0956 ($M^+ + 1$).

2,2-Bis(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile N^4-oxide (17a). To a stirred solution of 2,2-bis(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile (**16a**; 80 mg, 0.27 mmol) in 3 ml of CH_2Cl_2, *m*-CPBA (purity 70%, 104 mg , 0.42 mmol) was added at 0 °C. The mixture was stirred at room temperature for 15 h. The mixture was diluted with 5% sodium bicarbonate solution and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (CH_2Cl_2:MeOH = 95:5) to give 30 mg of 2,2-bis-(fluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-carbonitrile N^4-oxide (**17a**) in 36% yield.

Mp 204–207 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.63 (d, $J = 46$ Hz, 4H, C$\underline{H}_2$F), 5.89 (s, 1H, 3-H), 6.82–7.62 (m, 6H, arom. H), 8.13–8.47 (m, 1H, arom H). Anal. calcd for $C_{17}H_{12}N_2O_2F_2$: C, 64.97; H, 3.85; N, 8.91; found: C, 64.76; H, 4.02; N, 8.69. MS (EI) *m/z*: 314 (M^+).

The *N*-oxides (**17b**, **17c**, and **17d**) were prepared from the pyridines (**16b**, **16c**, and **16d**), respectively, in a similar manner to **17a**.

2-[2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (17b). Mp 183–184 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.65 (d, $J = 46$ Hz, 4H, C$\underline{H}_2$F), 5.95 (s, 1H, 3-H), 7.00 (d, $J = 8$ Hz, 1H, arom. H), 7.35–7.88 (m, 4H, arom. H), 8.07 (dd, 1H, arom. H), 8.20–8.50 (m, 1H, arom. H). Anal. calcd for $C_{16}H_{12}N_2O_4F_2$: C, 57.49; H, 3.62; N, 8.38; found: C, 57.27; H, 3.66; N, 8.27. MS (EI) *m/z*: 334 (M^+).

2-[2,2-Bis(fluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (17c). Mp 169–170 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 4.51–4.84 (m, 4H, C$\underline{H}_2$F), 5.91 (s, 1H, 3-H), 6.95 (d, $J = 1.7$ Hz, 1H, arom. H), 7.03 (d, $J = 8.3$ Hz, 1H, arom. H), 7.34–7.42 (m, 3H, arom. H), 7.46 (dd, $J = 1.7, 8.3$ Hz, 1H, arom. H), 8.32–8.35 (m, 1H, arom. H). Anal. calcd for $C_{17}H_{12}NO_2F_5$: C, 57.15; H, 3.39; N, 3.92; found: C, 57.28; H, 3.51; N, 3.89. MS (EI) *m/z*: 357 (M^+).

2-[6-Pentafluoroethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (17d). Mp 105–107 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 4.63 (d, $J = 46$ Hz, 4H, $C\underline{H}_2F$), 5.88 (s, 1H, 3-H), 6.87 (d, $J = 2$ Hz, 1H, arom. H), 6.99 (d, $J = 8$ Hz, 1H, arom. H), 7.12–7.56 (m, 4H, arom. H), 8.06–8.41 (m, 1H, arom. H). Anal. calcd for $C_{18}H_{12}NO_2F_7$: C, 53.08; H, 2.97; N, 3.44; found: C, 53.29; H, 3.26; N, 3.37. MS (EI) *m*/*z*: 407 (M^+).

2,3-Dihydro-6-nitro-2,2-bis(trifluoromethyl)-4*H*-1-benzopyran-4-one (19b). To stirred solution of 2′-fluoro-5′-nitroacetophenone (**18**; 15.6 g, 85.2 mmol) and hexafluoroacetone trihydrate (22.5 g, 102 mmol) in 170 ml of benzene, pyrrolidine (8.5 ml, 102 mmol) was added at room temperature. The mixture was refluxed for 6 h while water was distilled off. The resulting mixture was diluted with CH_2Cl_2, washed with 2N HCl, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:CH_2Cl_2 = 1:1) to give 6.0 g of 2,3-dihydro-6-nitro-2,2-bis(trifluoromethyl)-4*H*-1-benzopyran-4-one (**19b**) in 21% yield.

Mp 109–110 °C (ethanol). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.27 (s, 2H, 3-H), 7.23 (d, $J = 9$ Hz, 1H, 8-H), 8.34 (dd, $J = 2$, 9 Hz, 1H, 7-H), 8.65 (d, $J = 2$ Hz, 1H, 5-H). Anal. calcd for $C_{11}H_5NO_4F_6$: C, 40.14; H, 1.53; N, 4.26; found: C, 39.86; H, 1.52; N, 4.38. MS (EI) *m*/*z*: 329 (M^+).

Compound **20b** was prepared from **19b** in a similar manner to trifluoromethanesulfonic acid 6-cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl ester.

Trifluoromethanesulfonic acid 2,2-bis(trifluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl ester (20b). Mp 60–61 °C (hexane). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.87 (s, 1H, 3-H), 7.13 (d, $J = 10$ Hz, 1H, 8-H), 8.14–8.39 (m, 2H, 5,7-H). Anal. calcd for $C_{12}H_4NO_6F_9S$: C, 31.25; H, 0.87; N, 3.04; found: C, 31.15; H, 0.85; N, 3.00. MS (EI) *m*/*z*: 461 (M^+).

2-[2,2-Bis(trifluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-pyridine (21b). To a solution of 2-bromopyridine (1.70 g, 10.8 mmol) in 40 ml of THF at −78 °C, *n*-BuLi (1.61 M hexane solution, 6.6 ml, 10.6 mmol) was added dropwise. After 30 min of stirring, a solution of $ZnCl_2$ (0.5 M THF solution, 21.3 ml, 10.7 mmol) was added to the mixture, then the reaction was stirred for 15 min, and the reaction was allowed to warm to 0 °C. To the mixture, $Pd(Ph_3P)_4$ (330 mg, 0.29 mmol) in 3 ml of THF and trifluoromethanesulfonic acid 2,2-bis(trifluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl ester (**20b**; 2.0 g, 4.3 mmol) in 10 ml of THF were added. After 2 h stirring at room temperature, the resulting mixture was shaken with H_2O, extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:ethyl acetate = 9:1) to obtain 1.25 g of 2-[2,2-bis(trifluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-pyridine (**21b**) in 74% yield.

Mp 108–109 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.91 (s, 1H, 3-H), 7.06 (d, $J = 9$ Hz, 1H, arom. H), 7.04–8.03 (m, 3H, arom. H), 8.18 (dd, $J = 2$, 9 Hz, 1H, arom. H), 8.39 (d, $J = 2$ Hz, 1H, arom. H), 8.58–8.77 (m, 1H, arom. H). Anal. calcd for $C_{16}H_8N_2O_3F_6$: C, 49.25; H, 2.07 N, 7.18; found: C, 49.27; H, 2.06; N, 7.16. MS (EI) *m*/*z*: 390 (M^+).

Compound **21e** was prepared from **21b** in a similar manner to **16e**.

2,2-Bis(trifluoromethyl)-4-(2-pyridinyl)-2*H*-1-benzopyran-6-amine. oil. ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 3.45 (brs, 2H, NH_2), 5.72 (s, 1H, 3-H), 6.34–6.88 (m, 3H, arom. H), 7.10–7.86 (m, 3H, arom. H), 8.52–8.61 (m, 1H, arom. H). MS (EI) *m*/*z*: 360 (M^+). HRMS (FAB) calcd for $C_{16}H_{11}N_2OF_6$: 361.0776 ($M^+ + 1$); found: 361.0742 ($M^+ + 1$).

2-[2,2-Bis(trifluoromethyl)-6-iodo-2*H*-1-benzopyran-4-yl]-pyridine (21e). Mp 93–94 °C (hexane–ether). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.74 (s, 1H, 3-H), 6.66 (d, $J = 8$ Hz, 1H, arom. H), 7.06–7.80 (m, 5H, arom. H), 8.45–8.68 (m, 1H, arom. H). Anal. calcd for $C_{16}H_8NOF_6I$: C, 49.79; H, 1.71 N, 2.97; found: C, 41.02; H, 1.68; N, 2.90. MS (EI) *m*/*z*: 471 (M^+).

2-[6-Cyano-2,2-bis(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine (21a). A stirred solution of 2-[2,2-bis(trifluoromethyl)-6-iodo-2*H*-1-benzopyran-4-yl]-pyridine (**21e**; 0.20 g, 0.43 mmol) and CuCN (0.05 g, 0.56 mmol) in 2 ml of DMF was stirred at 150 °C for 3 h. The mixture was diluted with H_2O and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, and evaporated. Chromatography of the resulting residue was carried out using silica gel (hexane:ethyl acetate = 10:1) to give 0.14 g of 2-[6-cyano-2,2-bis(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine (**21a**) in 86% yield.

Mp 108–109 °C (hexane-ether). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.91 (s, 1H, 3-H), 7.09 (d, $J = 8$ Hz, 1H, arom. H), 7.15–8.03 (m, 5H, arom. H), 8.63–8.84 (m, 1H, arom. H). Anal. calcd for $C_{17}H_8N_2OF_6$: C, 55.15; H, 2.18 N, 7.57; found: C, 55.24; H, 2.32; N, 7.52. MS (EI) *m*/*z*: 370 (M^+).

Compound **21c** was prepared from **21e** in a similar manner to **16c**.

2-[2,2-Bis(trifluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-pyridine (21c). Mp 80–81 °C (hexane). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.81 (s, 1H, 3-H), 7.00 (d, $J = 8$ Hz, 1H, arom. H), 7.01–7.09 (m, 5H, arom. H), 8.52–8.73 (m, 1H, arom. H). Anal. calcd for $C_{17}H_8NOF_9$: C, 49.41; H, 1.95 N, 3.38; found: C, 49.51; H, 2.00; N, 3.23. MS (EI) *m/z*: 413 (M^+).

Compound **21d** was prepared from **21e** in a similar manner to **16d**.

2-[6-Pentafluoroethyl-2,2-bis(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine (21d). Mp 94–95 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.95 (s, 1H, 3-H), 7.16 (d, $J = 8$ Hz, 1H, arom. H), 7.19–8.01 (m, 5H, arom. H), 8.61–8.87 (m, 1H, arom. H). Anal. calcd for $C_{18}H_8NOF_{11}$: C, 46.67; H, 1.74; N, 3.02; found: C, 46.86; H, 1.79; N, 3.09. MS (EI) *m/z*: 463 (M^+).

The *N*-oxides (**22a**, **22b**, **22c**, and **22d**) were prepared from the pyridines (**21a**, **21b**, **21c**, and **21d**), respectively, in a similar manner to **17a**.

2-[6-Cyano-2,2-bis(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (22a). Mp 160–161 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 5.93 (s, 1H, 3-H), 7.08 (d, $J = 1.4$ Hz, 1H, arom. H), 7.15 (d, $J = 6.4$ Hz, 1H, arom. H), 7.38– 7.50 (m, 3H, arom. H), 7.58 (dd, $J = 1.4$, 6.4 Hz, 1H, arom. H), 8.35 (d, $J = 4.6$ Hz, 1H, arom. H). Anal. calcd for $C_{17}H_8N_2O_2F_6$: C, 52.86; H, 2.09; N, 7.25; found: C, 52.78; H, 1.86; N, 7.34. MS (EI) *m/z*: 386 (M^+).

2-[2,2-Bis(trifluoromethyl)-6-nitro-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (22b). Mp 208–210 °C (hexane–ethyl acetate). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.96 (s, 1H, 3-H), 7.15 (d, $J = 10$ Hz, 1H, arom. H), 7.33–7.60 (m, 3H, arom. H), 8.16 (dd, $J = 3$, 10 Hz, 1H, arom. H), 8.25–8.46 (m, 1H, arom. H). Anal. calcd for $C_{16}H_8N_2O_4F_6$: C, 47.31; H, 1.98; N, 6.90; found: C, 47.24; H, 2.04; N, 6.92. MS (EI) *m/z*: 406 (M^+).

2-[2,2-Bis(trifluoromethyl)-6-trifluoromethyl-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (22c). Mp 123–125 °C (hexane). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.87 (s, 1H, 3-H), 6.93–7.65 (m, 6H, arom. H), 8.22–8.40 (m, 1H, arom. H). Anal. calcd for $C_{17}H_8NO_2F_9$: C, 47.57; H, 1.88; N, 3.26; found: C, 47.66; H, 1.88; N, 3.22. MS (EI) *m/z*: 429 (M^+).

2-[6-Pentafluoroethyl-2,2-bis(trifluoromethyl)-2*H*-1-benzopyran-4-yl]-pyridine 1-oxide (22d). Mp 98–99 °C (hexane). ^{1}H NMR ($CDCl_3$, 60 MHz) δ: 5.83 (s, 1H, 3-H), 6.81–7.52 (m, 6H, arom. H), 8.04–8.29 (m, 1H, arom. H). Anal. calcd for $C_{18}H_8NO_2F_{11}$: C, 45.11; H, 1.68; N, 2.92; found: C, 45.26; H, 1.77; N, 2.82. MS (EI) *m/z*: 479 (M^+).

Pharmacology. Vasorelaxant potency

Rats (Sprague–Dawley, male, 400–700 g) were killed by decapitation. The thoracic aorta was dissected out, immersed in cold Krebs-Henseleit (K-H) solution, and cleaned of surrounding connective tissues. The artery was cut into 2–3 mm long ring segments. Each ring was mounted under a resting tension of 2 g, in 10 ml organ bath containing a modified K-H solution of the following composition (mM): NaCl, 119; KCl, 4.8; $CaCl_2$, 2.53; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $NaHCO_3$, 24.8; glucose, 10. The solution was equilibrated with a gas mixture containing 95% O_2 and 5% CO_2. One side of the ring preparation was fixed to the bottom of the bath and the other end was connected by a hook to the level of a force-displacement transducer (Nihon Kohden, TB611T). Before experiments, all preparations were allowed to equilibrate for at least 1.5 hr at 37 °C. The artery rings were contracted by displacement of normal K-H solution to the K-H solution containing 30 mM KCl (high K + K−H solution). After the increased force of contraction had reached a plateau, test compounds were added cumulatively to obtain concentration-relaxation curves. Relaxation responses were calculated as percentages of reductions of the 30 mM KCl contraction. The intrinsic activity (IA) for each compound was calculated as the percentage of the maximum reduction. One concentration-relaxation curve was obtained for each preparation.

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