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6-Substituted 2,2-Bis(fluoromethyl)-benzopyran-4-carboxamide K^+ Channel Openers

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Abstract—In the course of our study to find an ideal antihypertensive potassium channel opener (KCO), *N*-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-carboxamide (**13f**, KC-515) showed a highly potent, slow and long-lasting antihypertensive effect with reduced reflex tachycardia, together with the beneficial effects of KCO such as improvement in lipid metabolism. These profiles identify KC-515 as a potential candidate. In conscious spontaneously hypertensive rats (SHR), the onset of the hypotensive effect of KC-515 (**13f**) was gradual and the maximum response was attained at around 6 h after dosing. The duration of action was over 18 h for 0.1 mg/kg. When administered to Zucker rats for 2 weeks with 0.03–0.3 mg/kg po range in the antihypertensive doses in hypertensive rat models, KC-515 (**13f**) significantly and dose-dependently reduced serum triglycerides to less than 70% of control without affecting total cholesterol.

Introduction

The purpose of antihypertensive therapy is not simply to lower blood pressure, but rather to reduce the increased risk of death and cardiovascular disease associated with hypertension.[1a] Although there are many cardiovascular risk factors, hypertension and hyperlipidemia are the major ones. Accordingly, ideal antihypertensive drugs should have favorable effects on these risk factors, especially on lipid metabolism, as well as good antihypertensive profile and reduced side effects for a good quality of life and good compliance. There is currently a large number of antihypertensive agents available.[1b] However, only α-blockers show beneficial effect on lipid metabolism.[1c]

Potassium channel openers (KCOs) produce membrane hyperpolarization by opening potassium channels[2a] followed by increasing potassium ions permeability, and thereby inhibit the influx of calcium ion through calcium channels and possibly inhibit release of calcium ions from intracellular stores.[2f] Prototype KCOs such as cromakalim (**1**), pinacidil (**2**), and Aplikalim (**3**) (Fig. 1) were shown to be potent antihypertensive agents,[2b,2c,2e] at least as effective as calcium channel blockers.[2b] In contrast to most antihypertensive medications, pinacidil (**2**) and levcromakalim (**1a**), an active enantiomer of cromakalim (**1**), improved the serum lipid profile,[2b] especially for patients with hyperlipidemia, possibly more markedly than α-blockers. In addition, KCOs were shown to ameliorate ischemia-induced cardiac damage, possibly by mimicking the ischemic preconditioning via opening of potassium channels.[2d,2g]

These results, together with other beneficial effects,[2d,2g,2h] suggest that KCOs may be candidates as ideal antihypertensive drugs with potential advantages over other antihypertensive drugs. However, the clinical utility of these prototype KCOs is hampered by the incidence of unwanted side effects due to acute peripheral vasodilation (headache, palpitations, edema, and flushing).[2h] They are considered to be associated with rapid increases in plasma levels after dosing. Thus, it is suggested that if the onset of the blood pressure lowering activity of KCOs is slow and if normalized blood pressure values persist throughout the therapeutic treatment, possible unwanted side effects due to reflex mechanisms may be minimized.[2d] In this context, a prodrug type compound Y-27152 (**4**), which is inactive in vitro and is gradually converted to its active form after oral administration, has been developed as an antihypertensive drug with a slow onset, a long duration of action, and less tachycardia, though the antihypertensive activity appeared to be somewhat lower than that of levcromakalim (**1a**).[3a,3b]

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In the course of our study to find an ideal antihypertensive KCO,[4a–m] we have investigated the synthesis of 6-substituted 2-fluoromethylbenzopyran-4-carboxamides and-4-carbothioamides, and observed *N*-(2-cyanoethyl)-2,2-bis(fluoromethyl)-6-pentafluoroethyl-2*H*-1-benzopyran-4-carboxamide (**13f**, KC-515) to be a potential candidate. In this paper, we report the synthesis and biological activity of 6-substituted 2-fluoromethylbenzopyran-4-carboxamides and 4-carbothioamides, and antihypertensive and lipid lowering activities of KC-515 (**13f**).

Chemistry

The compounds prepared in this study are listed in Tables 1 and 2 and their synthetic routes are outlined in Schemes 1–4. The starting material was 4-oxobenzopyran **6**, which was prepared from acetophenone **5** and 1,3-difluoroacetone.[5] Ketone **6** was reduced and subsequently dehydrated under acidic conditions to afford benzopyran **7**. Benzopyran **7** was transformed to 4-bromobenzopyran **8** by bromination and subsequent treatment with sodium hydroxide. Except for the 6-bromo compound, introduction of carboxyl group at the 4-position was accomplished by palladium-catalyzed hydroxycarbonylation in almost quantitative yield.[4g] The 6-nitro-4-carboxylic acid derivative **9j** was esterified and hydrogenated to afford the 6-amino derivative **10a** in quantitative yield. The amino group was diazotized and replaced by iodine atom to give **10k**. The 6-iodo compound **10k** was treated with potassium perfluoroalkanecarboxylate in the presence of copper(I) iodide in DMF and toluene to obtain the 6-perfluoroalkyl

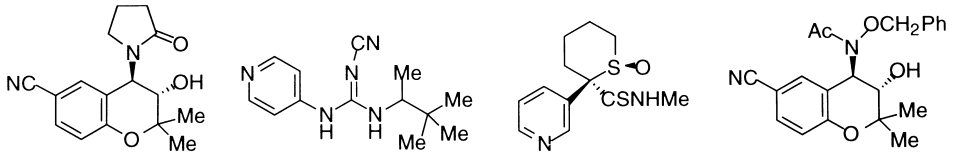
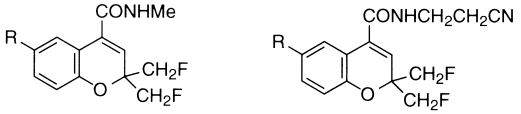


Figure 1.

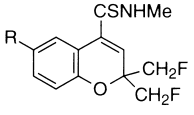
Table 1. Physical properties and vasorelaxant activities of 6-substituted 2,2-bis(fluoromethyl)benzopyran-4-carboxamides



Compd	R	Yield (%)[a]	Mp (°C)	Rat aorta		
				pEC_{50}[b]	IA (%)[c]	*n*[d]
12b	Br	88	187–188	7.24	75.9	2
12c	Cl	29	175–176	7.06	83.5	2
12d	H	42	138–139	5.77	82.9	2
12e	CF_3	86	162–164	7.81±0.05	66.8±1.2	3
12f	C_2F_5	74	128–129	8.14±0.06	63.7±4.2	3
12g	*n*-C_3F_7	77	88–91	7.91±0.11	67.2±1.7	3
12h	*n*-C_4F_9	63	Oil	6.65±0.03	80.9±2.6	3
12i	CN	95	206–207	7.08	73.4	2
12j[e]	NO_2	67	180–181	8.29±0.03	70.7±5.5	3
13a	NH_2·HCl	67	202–205	4.5 >		2
13b	Br	81	140–142	7.96	66.0	2
13c	Cl	39	134–136	7.76	75.1	2
13d	H	51	Oil	7.07	74.9	2
13e	CF_3	86	135–136	8.17±0.15	66.3±8.0	3
13f	C_2F_5	83	144–145	8.43±0.03	71.0±2.1	15
13g	*n*-C_3F_7	45	135–136	8.10±0.06	74.4±2.7	3
13h	*n*-C_4F_9	63	85–86	7.17±0.04	76.8±1.7	3
13i	CN	72	170–172	7.43	78.2	2
13j[e]	NO_2	85	179–180	8.65±0.03	72.3±8.7	3
Levcromakalim (**1a**)				6.97±0.05	72.5±3.6	8

[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 Experimental.
[c]Intrinsic activity ± SEM (%).
[d]Number of determinations.
[e]See ref 4f.

Table 2. Physical properties and vasorelaxant activities of 6-substituted 2,2-bis(fluoromethyl)benzopyran-4-carbothioamides



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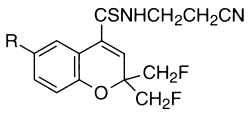

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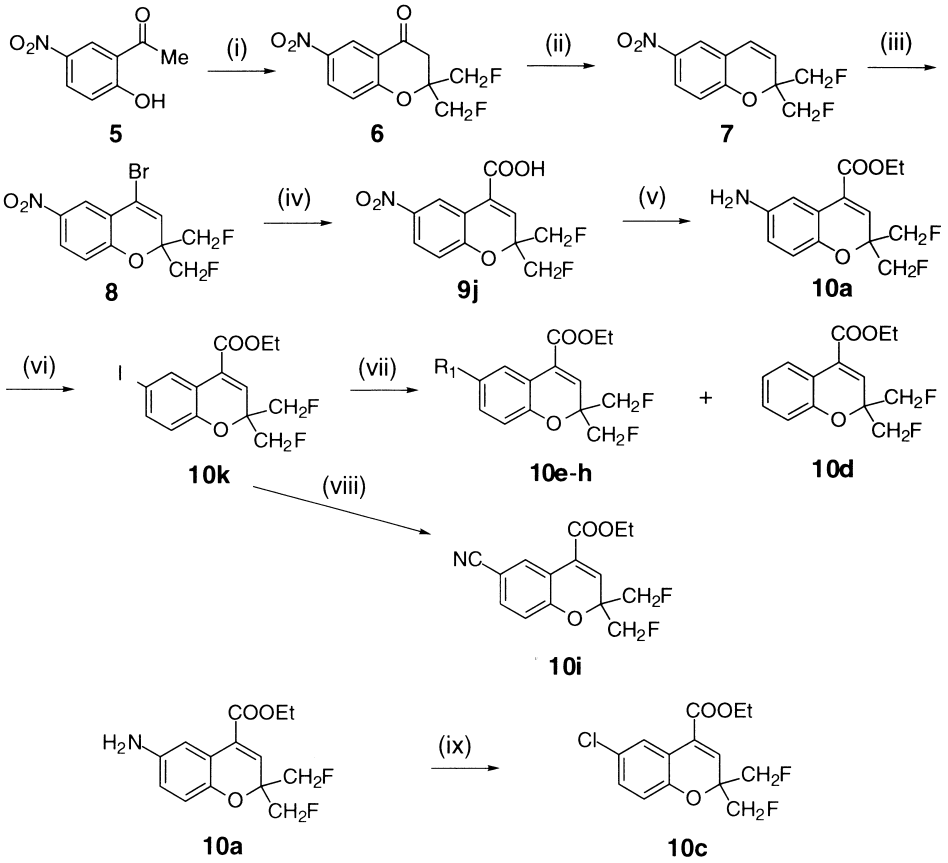
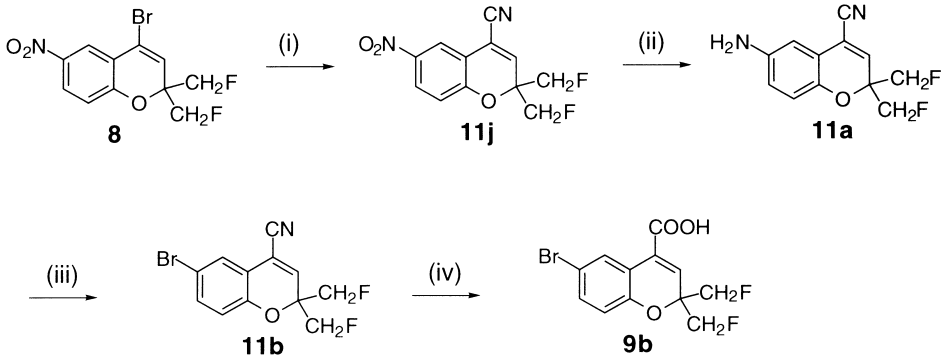
Compd	R	Yield (%)	Mp (°C)[a]	Rat aorta		
				pEC_{50}[b]	IA (%)[c]	n[d]
14e	CF_3	50	145–147	8.72	67.6	2
14f	C_2F_5	96	148–149	8.06	74.0	2
14g	n-C_3F_7	96	125–126	7.35	77.6	2
14i	CN	50	137–138	8.22	83.5	2
14j[e]	NO_2	96	134–135	9.32±0.11	74.5±8.9	3
15e	CF_3	52	105–106	8.64	66.8	2
15f	C_2F_5	62	108–109	8.03	72.8	2
15g	n-C_3F_7	44	94–95	7.63	58.0	2
15i	CN	55	191–192	8.17	82.3	2
15j[f]	NO_2	80	156–157	9.85±0.24	72.5±3.7	7
Levcromakalim (**1a**)				6.97±0.05	72.5±3.6	8

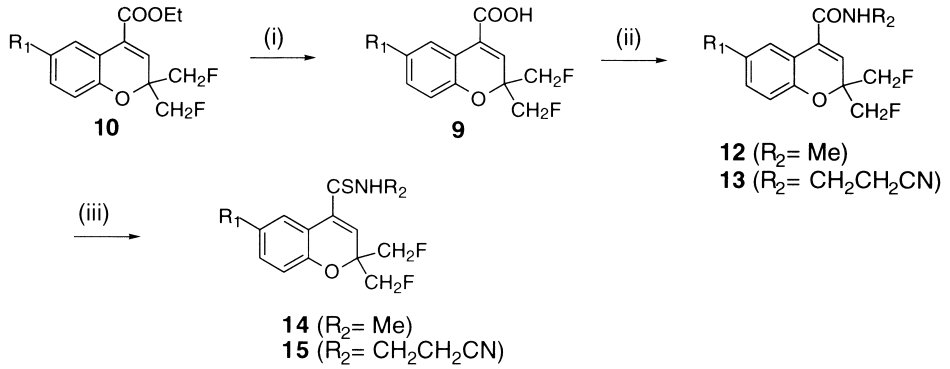
[a]Satisfactory microanalysis was obtained for all crystalline compounds.
[b]Negative logarithm of the molar concentration required to relax rat aorta precontracted with 30 mM KCl by 50% of IA, with ±SEM. Details are described in Experimental.
[c]Intrinsic activity ±SEM (%).
[d]Number of determinations.
[e]See ref 4f.
[f]See refs 4b and 4f.



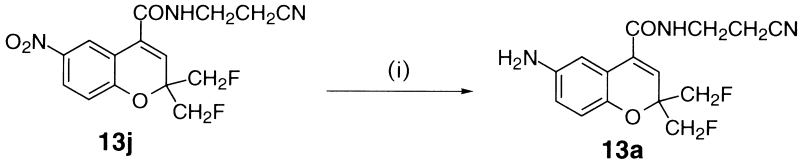
Scheme 1. (i) FCH_2COCH_2F, pyrrollidine, benzene (56%); (ii) (a) $NaBH_4$, MeOH; (b) *p*-TsOH, toluene (88%, 2 steps); (iii) (a) Br_2, $CHCl_3$; (b) 2 N NaOH, dioxane (quant.); (iv) CO_{gas} (balloon), $Pd(OAc)_2$, PPh_3, KOAc, KI, DMF (95%); (v) (a) H_2SO_4, EtOH; (b) H_2, Raney-Ni (W-1), EtOH (93%, 2 steps); (vi) (a) $NaNO_2$, H_2SO_4, H_2O–CH_2Cl_2; (b) KI, H_2O–CH_2Cl_2 (72%, 2 steps); (vii) R_1COOK ($R_1 = CF_3$, C_2F_5, C_3F_7), CuI, DMF–toluene or C_4F_9I, CuI, Cu, HMPA; (viii) CuCN, DMF (76%); (ix) (a) $NaNO_2$, H_2SO_4, H_2O–CH_2Cl_2; (b) CuCl; (c) H_2SO_4, EtOH (18% 3 steps).



Scheme 2. (i) CuCN, DMF (quant.); (ii) $SnCl_2$, EtOH; (iii) (a) $NaNO_2$, H_2SO_4–AcOH; (b) CuBr (42%, 3 steps); (iv) H_2SO_4, CaOH, H_2O (76%).



Scheme 3. (i) KOH, EtOH; (ii) CDI, R_2NH_2, THF; (iii) Lawesson's reagent, benzene or $ClCH_2CH_2Cl$.



Scheme 4. (i) (a) $SnCl_2$, EtOH; (b) HCl, MeOH (67%, 2 steps).

derivatives **10e–g**.[6] The 6-nonafluorobutyl compound **10h** was obtained by the alternative route. The iodo compound **10k** was treated with nonafluorobutyl iodide, copper(I) iodide, and copper in HMPA to produce **10h**. The deiodinated compound **10d** was obtained as a by-product under these conditions. The 6-cyano compound **10i** was converted from the 6-iodo compound **10k** by the reaction with copper(I) cyanide. The 6-chloro compound **10c** was synthesized by Sandmeyer reaction from the 6-amino compound **10a** using copper(I) chloride (Scheme 1).

In the case of 6-bromo derivatives, 4-bromo-6-nitrobenzopyran **8** was treated with copper(I) cyanide in DMF to afford 4-cyanobenzopyran (**11j**). The nitro group of **11j** was reduced by tin(II) chloride to yield 6-aminobenzopyran **11a**, and subsequently transformed to 6-bromo group by Sandmeyer reaction to obtain 6-bromo-4-cyanobenzopyran (**11b**), whose 4-cyano group was hydrolyzed under acidic conditions to afford 4-carboxylic acid **9b** (Scheme 2).

The ester group of **10** was hydrolyzed under alkaline conditions to yield the carboxylic acids **9**, and then activated with *N*,*N*′-carbonyldiimidazole (CDI), followed by addition of methylamine or 2-cyanoethylamine to give the carboxamide derivatives **12** and **13** (Scheme 3). The 6-amino derivative **13a** was synthesized from the corresponding 6-nitro derivative **13j** by reduction with tin(II) chloride in EtOH (67%) (Scheme 4). Thioamide derivatives **14** and **15** were obtained by thionation of carboxamide derivatives **12** and **13** with Lawesson's reagent in benzene or 1,2-dichloroethane (Scheme 3).

Results and Discussion

The vasorelaxant activities of compounds were determined by the effects on 30 mM KCl responses in rat isolated aorta in comparison with levcromakalim (**1a**)[7,8b] (Tables 1 and 2). The 2-fluoromethylbenzopyran-4-carboxamides **12** and **13** exhibited vasorelaxant activity comparable to or more potent than levcromakalim

(**1a**). The *N*-(2-cyanoethyl)carboxamide derivatives **13** had more potent vasorelaxant activity than the corresponding *N*-methylcarboxamide derivatives **12**. Increase in the size of the 6-perfluoroalkyl group of **12** and **13** gave a parabolic effect on the activity, the pentafluoroethyl group (**12f** and **13f**) being optimum. The most active compounds **13f** and **13j** showed some 30-fold more potent vasorelaxant activity than levcromakalim (**1a**) (Table 1). The 4-carbothioamides **14** and **15** exhibited vasorelaxant activity with potency greater than levcromakalim (**1a**). The SARs were somewhat different from those of the carboxamides **12**. The activity of *N*-methylcarbothioamide derivatives **14** was comparable to the *N*-(2-cyanoethyl)carbothioamide derivatives **15**. Increase in the size of the 6-perfluoroalkyl group of **14** and **15** reduced the activity, the trifluoromethyl group (**14e** and **15e**) being the most active. The 6-nitro derivatives **14j** and **15j** were the most potent compounds in this series (Table 2). Among these compounds, some compounds were selected for further study from some preclinical studies.

Antihypertensive effects of KC-515 (**13f**) and **15j** (KC-399)[4b] were evaluated in conscious spontaneously hypertensive rats (SHR) in comparison with levcromakalim (**1a**) (Figs 2 and 3). KC-515 (**13f**) at 0.01–0.1 mg/kg po produced dose-dependent falls in mean blood pressure (MBP). The onset of the hypotensive effect of KC-515 (**13f**) was gradual and the maximum response attained at around 6 h after dosing. The duration of action was over 18 h for 0.1 mg/kg. But, the effects on the heart rate were minimal. In contrast, the hypotensive effect of levcromakalim (**1a**) (0.1 and 0.3 mg/kg po) was rapid in onset and of short duration of action (Fig. 3). Unlike KC-515 (**13f**), levcromakalim (**1a**) dramatically increased heart rate in a dose-dependent manner. Thus, KC-515 (**13f**) was some 10-fold more potent than levcromakalim (**1a**) in lowering blood pressure, with slower onset, longer duration of action, and less tachycardia. KC-515 (**13f**) (0.01–0.1 mg/kg po) also produced dose-dependent antihypertensive effects with a slow onset, a long duration of action, and less tachycardia, in two kidney–one clip renal hypertensive rats and DOCA-salt hypertensive rats, similar to the effects seen in SHR.[8a] KC-399 (**15j**) also showed a highly potent, slow and long-lasting antihypertensive effects with reduced reflex tachycardia. However, KC-399 (**15j**) was dropped out in toxicological test.

One of the most interesting features of antihypertensive KCOs is the beneficial effect on plasma lipids.[2h] The lipid lowering effect of KC-515 (**13f**) was evaluated in obese Zucker rats, a genetic model of hyperlipidemia. When administered to Zucker rats for 2 weeks with 0.03–0.3 mg/kg po range in the antihypertensive doses in hypertensive rat models, KC-515 (**13f**) significantly and dose-dependently reduced serum triglycerides to less than 70% of control (32, 33, and 46% decreases, respectively, for 0.03, 0.1, and 0.3 mg/kg po dosing), without affecting total cholesterol (Tables 3 and 4).[8a]

Thus, as an antihypertensive agent, KC-515 (**13f**) possesses several properties which confer advantages over other antihypertensive drugs including the prototype KCOs. KC-515 (**13f**) was shown to be an ATP-sensitive KCO, because it strongly inhibited contraction of rat aortic rings established with 30 mM KCl, while it produced only small inhibitory effects against rat aortic rings contracted with 90 mM KCl, it accelerated $^{86}Rb^{+}$ efflux from isolated rat aorta, and these effects were antagonized by glibenclamide, an ATP-sensitive potassium channel blocker.[8b] Further studies on other beneficial effects of KC-515 (**13f**) are now under way.

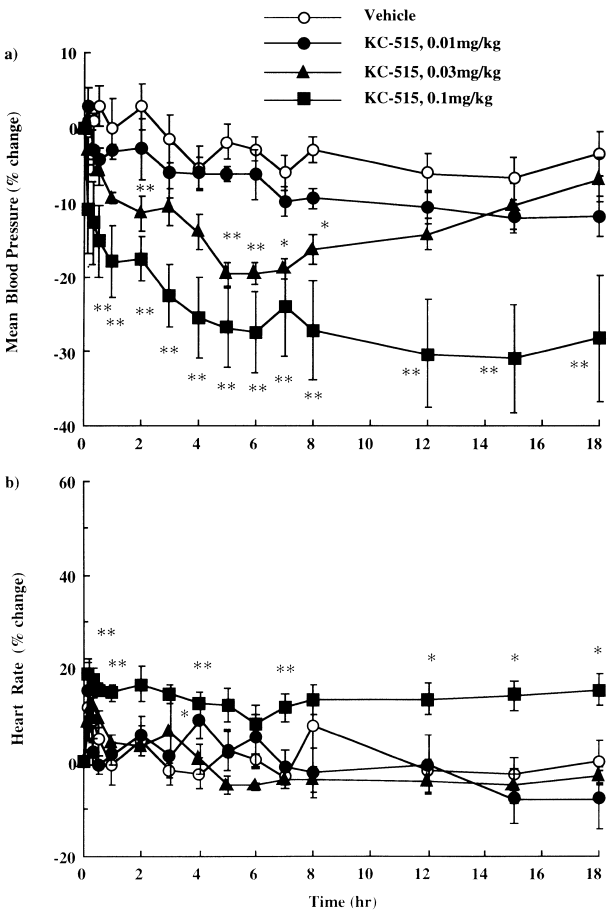


Figure 2. Effects of orally administered KC-515 (**13f**) on (a) mean blood pressure (% change) and (b) heart rate (% change) at various time intervals (h) in conscious male SHR. Pretreatment values for blood pressure (mm Hg) and heart rate (beat/min) were 155±5 ($n=5$) and 330±8 ($n=5$) for control, 158±5 ($n=5$) and 388±20 ($n=5$) for KC-515 (0.01 mg/kg), 158±7 ($n=5$) and 324±14 ($n=5$) for KC-515 (0.03 mg/kg), and 157±6 ($n=5$) and 350±9 ($n=5$) for KC-515 (0.1 mg/kg) groups, respectively. There was no significant difference between groups. Each value represents mean ±SE ($n=5$). $*P<0.05$, $**P<0.01$, significant difference from controls. Details are described in Experimental.

Conclusion

KC-515 (**13f**) shows a highly potent, slow and long-lasting antihypertensive effect with reduced reflex tachycardia, together with the beneficial effects of KCO such as improvement in lipid metabolism. These profiles identify KC-515 as a potential candidate for an ideal antihypertensive drug.

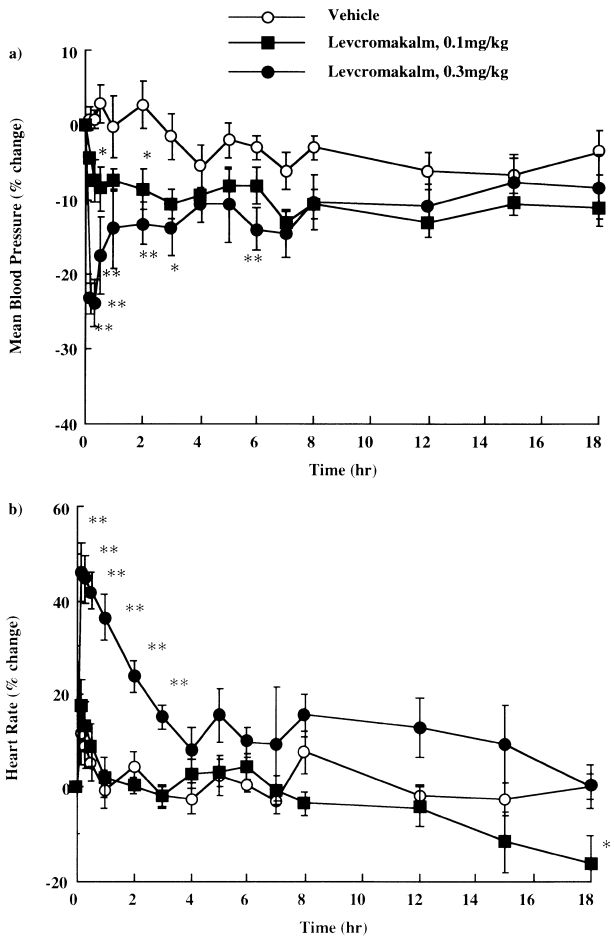


Figure 3. Effects of orally administered levcromakalim (**1a**) on (a) mean blood pressure (% change) and (b) heart rate (% change) at various time intervals (h) in conscious male SHR. Pretreatment values for blood pressure (mm Hg) and heart rate (beat/min) were 155±5 ($n=5$) and 330±8 ($n=5$) for control, 161±3 ($n=5$) and 394±15 ($n=5$) for levcromakalim (0.1 mg/kg), 158±3 ($n=5$) and 340±16 ($n=5$) for levcromakalim (0.3 mg/kg) groups, respectively. There was no significant difference between groups. Each value represents mean ±SE ($n=5$). $*P<0.05$, $**P<0.01$, significant difference from controls. Details are described in Experimental.

Experimental

General

Melting points were determined on a Yanagimoto micro melting point apparatus and are recorded. ^{1}H NMR spectra were recorded on a Hitachi R-24B (60 MHz) or a JEOL FX-270 (270 MHz) instrument. Coupling constants are reported in hertz (Hz) and chemical shifts in ppm (units) downfield from internal tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad. Mass spectra (MS) were recorded on a Shimadzu GCMS-QP-1000 mass spectrometer. Elemental analyses were performed at Toray research center. Where represented by elemental symbols, the analyses of these elements fall within ±0.4% of the calculated values. Column chromatographies were performed with silica gel, Wakogel C-200 (0.074–0.149 mm). HPLC analyses were performed on a Hitachi L-4000 detector with a Hitachi L-6200 pump, the column was a YMC-Pack A-312 S-5 120A ODS.

Biological test: effects on KCl induced contraction

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 a 10 mL organ bath containing a modified K–H solution of the following composition (mL): 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 at the level of a force–displacement transducer (Nihon Koden, TB611T). Before the initiation of the experiments, all preparations were allowed to equilibrate for at least 1.5 h 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 in a cumulative way to construct concentration–relaxation curves. Relaxation responses were calculated as percentage of reductions of the 30 mM KCl contraction. The intrinsic activity (IA) for each compound was calculated as a percentage of its maximum reduction of the 30 mM KCl contraction. Only one concentration–relaxation curve was obtained from each preparation.

Biological test: effects on mean blood pressure

Male spontaneously hypertensive rats (SHR) (16–24 weeks old, about 350 g) purchased from Charles River Japan (Atsugi, Japan) were anesthetized with an ip

Table 3. Effects of KC-515 (0.3 mg/kg) on plasma lipids following 2 weeks administration with single daily doses in Zucker rats[a]

	Vehicle ($n=6$)	Levcromakalim ($n=5$)		KC-515 ($n=5$)
		1.0 mg/kg	10 mg/kg	0.3 mg/kg
Total cholesterol (TC) (mg/dl serum)	88.00±4.99	115.62±5.84**	130.46±6.33**	122.86±5.59**
HDL (mg/dl serum)	67.98±3.21	90.88±4.02**	97.28±4.99**	90.16±4.39**
HDL/TC (%)	77.59±1.96	78.77±1.46	74.54±0.69	73.37±1.11
Triglyceride (mg/dl serum)	189.07±27.45	158.44±15.86	124.40±7.34*	112.42±9.70*

[a]All data shown as the mean±SEM. Asterisks indicate significant difference ($*P<0.05$; $**P<0.01$) from vehicle.

Table 4. Effects of KC-515 (0.03, 0.1 mg/kg) on plasma lipids following 2 weeks administration with single daily doses in Zucker rats[a]

	Vehicle ($n=5$)	Bezafibrate ($n=5$) 50 mg/kg	KC-515 ($n=5$)	
			0.03 mg/kg	0.1 mg/kg
Total cholesterol (TC) (mg/dl serum)	106.00±10.67	79.92±2.32	116.52±18.31	127.08±7.99
HDL (mg/dl serum)	70.63±6.23	55.12±2.60	84.22±12.99	93.40±4.49
HDL/TC (%)	66.92±1.82	69.03±3.01	72.47±0.95	73.93±2.63
Triglyceride (mg/dl serum)	351.18±28.87	277.62±26.02	246.60±22.27*	260.28±21.41*

[a]All data shown as mean±SEM. Asterisks indicate significant difference (*$P<0.05$; **$P<0.01$) from vehicle.

injection of pentobarbital Na (50 mg/kg). The right femoral artery was dissected free from the surrounding tissue and a polyethylene tubing filled with heparin (1000 U/mL) was inserted into the abdominal aorta through the femoral artery for the measurement of blood pressure and heart rate. The tubing was tunneled subcutaneously and exteriorized between the scapulae. After surgery, rats were housed individually and allowed to recover overnight. Blood pressure was measured with a Nihon Kohden pressure transducer (DX-312) and the heart rate with a Nihon Kohden heart rate counter (AT-601G) in unanesthetized and unrestrained conditions. All recordings were made on a chart with a Graphtech linearcorder (WR-3101). Drugs were suspended with 0.3% carbomethylcellulose. The drug solution or vehicle was given in a volume of 1 mL/kg.

Biological test: effects on lipid metabolism

Drugs were suspended with 0.3% carbomethylcellulose. The drug solution or vehicle was given in a volume of 1 mL/kg. The drug solution (30, 100, 300 μg/kg/day) or vehicle were administered to Zucker rats (14 weeks) for 2 weeks. After oral administration of the experiment for 2 weeks, blood was sampled from each animal. Plasma cholesterol and triglycerides (TG) were measured by autoanalyzer (COBAS-FARA II).

Synthesis of compounds

2,2-Bis(fluoromethyl)-3,4-dihydro-6-nitro-2*H*-1-benzopyran-4-one (6). Pyrrolidine (50 mL, 0.6 mol) was added to a solution of 6′-hydroxy-3′-nitroacetophenone (108 g, 0.6 mol) and, 2,2-bis(fluoromethyl)acetone (70 g, 0.6 mol) in benzene (1.2 L), and the mixture was stirred at room temperature for 1.5 h, and then heated under reflux for 1 h. After cooling down to room temperature, the mixture was then poured into water, the product was extracted with AcOEt, and the extract was dried (Na_2SO_4), and evaporated. The residual oil was chromatographed on silica gel (hexane:CH_2Cl_2, 1:1) to give pure **6** (86.0 g, 56%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.99 (2H, s, C-3H), 4.60 (4H, d, $J_{H\text{-}F}=47.0$ Hz, C-2H), 7.10 (1H, d, $J=9.0$ Hz, C-8H), 8.28 (1H, dd, $J=9.0$, 3.0 Hz, C-7H), 8.65 (1H, d, $J=3.0$ Hz, C-5H); mp 133–134 °C (EtOH); MS (EI) m/z 257 (M^+); anal. ($C_{11}H_9F_2NO_4$) C, H, N.

2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran (7). Sodium borohydride (30 g, 0.74 mol) was added to a stirred suspension of **6** (114 g, 0.44 mol) in MeOH (800 mL) and THF (500 mL) at −10 °C and the mixture was maintained at this temperature for 40 min; 3 N HCl was added and the product was extracted with CH_2Cl_2. The organic layer was washed with 0.5 N NaOH, 3 N HCl, dried (Na_2SO_4), and evaporated under reduced pressure to afford a crude alcohol, which was used without further purification. A mixture of the crude alcohol and *p*-toluenesulfonic acid monohydrate (12.0 g, 0.63 mol) in toluene (1 L) was heated at reflux for 1.5 h. The reaction mixture was then cooled, washed with 0.5 N NaOH, brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give **7** (93.8 g, 88%) .

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.52 (4H, d, $J_{H\text{-}F}=47.0$ Hz, C-2H), 5.77 (1H, d, $J=10.0$ Hz, C-3H), 6.69 (1H, d, $J=10.0$ Hz, C-4H), 6.92 (1H, d, $J=9.0$ Hz, C-8H), 7.8–8.2 (2H, m, C-5H, C-7H); mp 125–126 °C (AcOEt:hexane); MS (EI) m/z 241 (M^+); anal. ($C_{11}H_9F_2NO_3$) C, H, N.

4-Bromo-2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran (8). Bromine (62 mL, 1.20 mol) was added dropwise to a solution of **7** (93.8 g, 0.39 mol) in chloroform (1.0 L) at −10 °C, and the mixture was stirred at −10 °C for 12 h. The reaction mixture was washed with aqueous $NaHCO_3$, 1 N NaOH, dried (Na_2SO_4), and evaporated under reduced pressure to give crude dibromide. It was taken to the next step without purification.

A mixture of crude dibromide, dioxane (1.0 L), and 2 N NaOH (300 mL) was stirred at −10 °C for 2.5 h. The reaction mixture was poured into H_2O (2.5 L), and the resulting crystal was isolated by filtration. The crystal was dissolved in CH_2Cl_2, the organic layer was dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to **8** (119.2 g, quant.).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.48 (4H, d, $J_{H\text{-}F}=47.0$ Hz, C-2H), 6.12 (1H, s, C-3H), 6.88 (1H, d, $J=9.0$ Hz, C-8H), 8.04 (1H, dd, $J=9.0$, 2.0 Hz, C-7H), 8.24 (1H, d, $J=2.0$ Hz, C-5H); mp 117–118 °C (AcOEt:hexane); MS (EI) m/z 319 (M^+); anal. ($C_{11}H_8BrF_2NO_3$) C, H, N.

2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-carboxylic acid (9j). A mixture of **8** (640 mg, 2.0 mmol), $Pd(OAc)_2$ (5.0 mg, 0.022 mmol), PPh_3 (11.0 mg, 0.042

mmol), potassium acetate (800 mg, 8.15 mmol) and potassium iodide (330 mg, 1.99 mmol) in DMF (10 mL) was stirred under a CO balloon at 130 °C for 3 h. The reaction mixture was diluted with water, acidified with 2 N HCl, and extracted with AcOEt. The organic extracts was washed with brine, and extracted with 2 N NaOH. The aqueous alkaline extracts were acidified with 2 N HCl, and extracted with AcOEt. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was chromatographed on silica gel with MeOH:AcOH:$CHCl_3$ (5:1:500) to **9j** (540 mg, 95%).

270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.64 (4H, d, $J_{H\text{-}F}$ = 46.5 Hz, C-2H), 6.88 (1H, s, C-3H), 7.03 (1H, d, J = 8.90 Hz, C-8H), 8.14 (1H, dd, J = 8.90, 2.64 Hz, C-7H), 9.09 (1H, d, J = 2.64 Hz, C-5H); mp 174–175 °C (AcOEt: hexane); MS (EI) m/z 285 (M^+); anal. ($C_{12}H_9F_2NO_5$) C, H, N.

2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10j). A mixture of **9j** (41.7 g, 146 mmol), EtOH (300 mL), and concd H_2SO_4 (20 mL) was refluxed for 7 h. The mixture was poured into ice–water, and the resulting crystal was isolated by filtration. The crystal was dissolved in AcOEt and ether, the organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was chromatographed on silica gel with hexane:AcOEt (5:1) to **10j** (21.4 g, 93%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.42 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.38 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.58 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 6.69 (1H, s, C-3H), 6.94 (1H, d, J = 9.0 Hz, C-8H), 8.07 (1H, dd, J = 9.0, 3.0 Hz, C-7H), 8.92 (1H, d, J = 3.0 Hz, C-5H); mp 96–98 °C (AcOEt); MS (EI) m/z 313 (M^+); anal. ($C_{14}H_{13}F_2NO_5$) C, H, N.

6-Amino-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10a). A mixture of **10j** (11.7 g, 37.3 mmol), Raney Ni (W-1) (12.0 g), and EtOH (330 mL) was stirred under a hydrogen atmosphere. After the completion of the hydrogenation, the catalyst was removed by filtration, and the solvent was removed in vacuo to yield **10a** (10.5 g, quant.).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.38 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.30 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.56 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.43–7.43 (4H, m, C-3H, C-5H, C-7H, C-8H). MS (EI) m/z 283 (M^+); colorless oil.

6-Iodo-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10k). A mixture of **10a** (3.0 g, 10 mmol), concd H_2SO_4 (1.2 g, 12 mmol), CH_2Cl_2 (50 mL), and H_2O (40 mL) was cooled to 0 °C. Sodium nitrate (0.77 g, 11 mmol) in H_2O (5 mL) was added to the mixture, and the mixture was stirred for 10 min at 0 °C. A mixture of potassium iodide (2.0 g, 1.2 mmol) in H_2O (5 mL) was added to the reaction mixture, and stirred for 50 min at room temperature. The product was extracted with CH_2Cl_2. The organic extracts were washed with aqueous Na_2SO_3, brine, dried (Na_2SO_4), and evaporated under vacuum. The residue was chromatographed on silica gel with hexane:AcOEt (10:1) to **10k** (3.03 g, 72%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS): δ 1.38 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.32 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.54 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.58 (1H, s, C-3H), 6.65 (1H, d, J = 9.0 Hz, C-8H), 7.50 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.30 (1H, d, J = 2.0 Hz, C-5H); mp 89–90 °C (AcOEt:hexane); MS (EI) m/z 394 (M^+); anal. ($C_{14}H_{13}F_2IO_3$) C, H, N.

2,2-Bis(fluoromethyl)-6-(trifluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10e). A mixture of **10k** (1.00 g, 2.5 mmol), potassium trifluoroacetate (0.84 g, 5.5 mmol), copper(I) iodide (1.18 g, 6.0 mmol), toluene (4 mL), and DMF (10 mL) was heated at 150 °C for 4 h under nitrogen atmosphere with Dean–Stark trap, and heated at 160 °C for 1.5 h. After cooling down to room temperature, 2 N HCl and AcOEt were added to the mixture, and the mixture was filtered through Celite. The organic layer was separated from the filtrate, and the aqueous layer was extracted with AcOEt. The resulting organic layers were combined, washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel with hexane:AcOEt (10:1) to **10e** (0.51 g, 60%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.36 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.31 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.53 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.63 (1H, s, C-3H), 6.94 (1H, d, J = 9.0 Hz, C-8H), 7.47 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.31 (1H, d, J = 2.0 Hz, C-5H); MS (EI) m/z 336 (M^+); colorless oil.

2,2-Bis(fluoromethyl)-6-(pentafluoroethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10f). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.40 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.38 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.60 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.69 (1H, s, C-3H), 7.00 (1H, d, J = 9.0 Hz, C-8H), 7.45 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.30 (1H, d, J = 2.0 Hz, C-5H); MS (EI) m/z 386 (M^+); yield 64%; colorless oil.

2,2-Bis(fluoromethyl)-6-(heptafluoropropyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10g). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.36 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.32 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.57 (4H, d, $J_{H\text{-}F}$ = 48.0 Hz, C-2H), 6.69 (1H, s, C-3H), 7.02 (1H, d, J = 9.0 Hz, C-8H), 7.46 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.29 (1H, d, J = 2.0 Hz, C-5H); MS (EI) m/z 436 (M^+); yield 75%.

2,2-Bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10d). Compound **10d** was obtained as a minor product in the reaction of **10g**.

60 MHz ^{1}H NMR ($CDCl_3$, TMS): δ 1.37 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.33 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.58 (4H, d, $J_{H\text{-}F}$ = 49.0 Hz, C-2H), 6.58 (1H, s, C-3H), 6.74–8.11 (4H, m, C-5H, C-6H, C-7H, C-8H); MS (EI) m/z 268 (M^+); yield 25%; colorless oil.

2,2-Bis(fluoromethyl)-6-(nonafluorobutyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10h). A mixture of **10k** (0.30 g, 0.76 mmol), nonafluorobutyl iodide (3.5 g, 10 mmol), copper (0.30 g, 4.8 mmol), copper(I) iodide (0.32 g, 1.67 mmol), and hexamethylphosphoramide (HMPA) (3 mL) was stirred for 22 h at 80 °C under nitrogen atmosphere. Nonafluorobutyl iodide (0.8 mL, 4.76 mmol) was added and stirred at 130 °C for 2 h, and nonafluorobutyl iodide (0.4 mL, 2.38 mmol) was added and stirred at 155 °C for 3 h. After cooling down to room temperature, 2 N HCl and AcOEt were added to the mixture, and the mixture was filtered through Celite. The organic layer was separated from the filtrate, and the aqueous layer was extracted with AcOEt. The organic extracts were washed with aqueous Na_2SO_3, brine, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with hexane:AcOEt (5:1) to give **10h** (0.19 g, 51%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.38 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.36 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.59 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.68 (1H, s, C-3H), 7.01 (1H, d, J = 9.0 Hz, C-8H), 7.48 (1H, dd, J = 9.0, 3.0 Hz, C-7H), 8.30 (1H, d, J = 3.0 Hz, C-5H); MS (EI) m/z 486 (M^+); colorless oil.

6-Cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10i). A mixture of **10k** (0.40 g, 1.0 mmol), copper(I) cyanide (0.11 g, 1.1 mmol), and DMF (3 mL) was stirred at 160 °C for 2.5 h. After cooling down to room temperature, 2 N HCl was added to the mixture the mixture was extracted with AcOEt. The organic extracts were washed with brine, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with hexane:AcOEt (3:1) to give **10i** (0.22 g, 76%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.34 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.31 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.54 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.68 (1H, s, C-3H), 6.90 (1H, d, J = 9.0 Hz, C-8H), 7.45 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.33 (1H, d, J = 2.0 Hz, C-5H); mp 115–117 °C (AcOEt:hexane); MS (EI) m/z 293 (M^+); anal. ($C_{15}H_{13}F_2NO_3$) C, H, N.

6-Chloro-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid ethyl ester (10c). A mixture of **10a** (0.52 g, 1.84 mmol), concd HCl (0.5 mL), and EtOH (15 mL) was stirred for 0.5 h at room temperature. The mixture was concentrated in vacuo to give hydrochloric acid salt of **10a**.

A mixture of the hydrochloric acid salt of **10a** (0.41 g, 1.28 mmol), H_2O (10 mL) and concd H_2SO_4 (0.13 g, 1.28 mmol) was cooled to 0 °C. An aqueous solution (10 mL) of sodium nitrite (0.10 g, 1.45 mmol) was added dropwise with stirring. Stirring was continued for 1 h at 0 °C. The reaction mixture was added dropwise to a mixture of copper chloride (0.25 g, 2.56 mmol) and concd HCl (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, at room temperature for 3 h, and heated at 70 °C for 3 h. After cooling down to room temperature, the reaction mixture was extracted with AcOEt, and the organic layer was extracted with 2 N NaOH. The alkaline extracts was acidified with concd HCl, and extracted with AcOEt. The AcOEt layer was washed with brine, dried (Na_2SO_4), evaporated to give a crude mixture of an ester and a carboxylic acid, which was used without further purification. A mixture of the crude products, EtOH (50 mL) and concd H_2SO_4 (2 mL) was refluxed for 2 h. After cooling down to room temperature, the reaction mixture was evaporated, and H_2O was added to the residue, extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with hexane:AcOEt (10:1) to give **10c** (0.07 g, 18%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 1.37 (3H, t, J = 7.0 Hz, $COOCH_2CH_3$), 4.31 (2H, q, J = 7.0 Hz, $COOCH_2$), 4.54 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.62 (1H, s, C-3H), 6.81 (1H, d, J = 9.0 Hz, C-8H), 7.18 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.98 (1H, d, J = 2.0 Hz, C-5H); mp 76–78 °C (Et_2O:hexane); MS (EI) m/z 302 (M^+); anal. ($C_{14}H_{13}ClF_2O_3$) C, H, N.

2,2-Bis(fluoromethyl)-6-(trifluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid (9e). A mixture of **10e** (0.51 g, 1.52 mmol), potassium hydroxide (0.13 g, 2.0 mmol), and EtOH (10 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into ice-cooled aqueous HCl. The resulting crystals were isolated by filtration, and washed with H_2O. The crystals were dissolved in CH_2Cl_2, the organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give **9e** (0.43 g, 92%).

270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.63 (4H, $J_{H\text{-}F}$ = 46.9 Hz, C-2H), 6.91 (1H, s, C-3H), 7.03 (1H, d, J = 8.57 Hz, C-8H), 7.52 (1H, dd, J = 8.57, 1.64 Hz, C-7H), 8.36 (1H, d, J = 1.64 Hz, C-5H); mp 162–163 °C (AcOEt:hexane); MS (EI) m/z 308 (M^+); anal. ($C_{13}H_9F_5O_3$) C, H, N.

2,2-Bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid (9d). 270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.60 (4H, $J_{H\text{-}F}$ = 46.9 Hz, C-2H), 6.77 (1H, s, C-3H), 6.93–7.28 (3H, m, C-6H, C-7H, C-8H), 7.93 (1H, d, J = 7.58 Hz, C-5H); MS (EI) m/z 240 (M^+); yield 85%; colorless oil.

2,2-Bis(fluoromethyl)-6-(pentafluoroethyl)-2*H*-1-benzopyran-4-carboxylic acid (9f). 270 MHz ^{1}H NMR ($CDCl_3$–acetone-d_6, TMS) δ 4.62 (4H, $J_{H\text{-}F}$ = 46.5 Hz, C-2H), 6.81 (1H, s, C-3H), 7.02 (1H, d, J = 8.57 Hz, C-8H), 7.45 (1H, dd, J = 8.57, 1.98 Hz, C-7H), 8.42 (1H, d, J = 1.98 Hz, C-5H); mp 173–174 °C (AcOEt:hexane); MS (EI) m/z 358 (M^+); anal. ($C_{14}H_9F_7O_3$) C, H, N; yield quant.

2,2-Bis(fluoromethyl)-6-(heptafluoropropyl)-2*H*-1-benzopyran-4-carboxylic acid (9g). 270 MHz ^{1}H NMR ($CDCl_3$, TMS): δ 4.63 (4H, $J_{H\text{-}F}$ = 46.5 Hz, C-2H), 6.92 (1H, s, C-3H), 7.05 (1H, d, J = 8.57 Hz, C-8H), 7.47 (1H, dd, J = 8.57, 1.65 Hz, C-7H), 8.32 (1H, d, J = 1.65 Hz, C-5H); mp 162–163 °C (AcOEt:hexane); MS (EI) m/z 408 (M^+); anal. ($C_{15}H_9F_9O_3$) C, H, N; yield 96%.

2,2-Bis(fluoromethyl)-6-(nonafluorobutyl)-2*H*-1-benzopyran-4-carboxylic acid (9h). 270 MHz ^{1}H NMR

($CDCl_3$–acetone-d_6, TMS) δ 4.62 (4H, $J_{H\text{-}F}$ = 46.5 Hz, C-2H), 6.82 (1H, s, C-3H), 7.03 (1H, d, J = 8.57 Hz, C-8H), 7.45 (1H, dd, J = 8.58, 1.65 Hz, C-7H), 8.40 (1H, d, J = 1.65 Hz, C-5H); mp 180–181 °C (AcOEt:hexane); MS (EI) m/z 458 (M^+); anal. ($C_{16}H_9F_{11}O_3$) C, H, N; yield 84%.

6-Cyano-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid (9i). 270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.63 (4H, $J_{H\text{-}F}$ = 46.9 Hz, C-2H), 6.95 (1H, s, C-3H), 7.02 (1H, d, J = 8.25 Hz, C-8H), 7.55 (1H, dd, J = 8.28, 1.98 Hz, C-7H), 8.46 (1H, d, J = 1.98 Hz, C-5H); mp 165–167 °C (AcOEt:hexane); MS (EI) m/z 265 (M^+). anal. ($C_{13}H_9F_2NO_3$) C, H, N; yield 79%.

2,2-Bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-carbonitrile (11j). A mixture of **8** (20.2 g, 63.1 mmol), copper(I) cyanide (6.2 g, 69.2 mmol) and DMF (200 mL) was refluxed for 6 h. The reaction mixture was poured into ice-cooled 2 N HCl the resulting crystals were isolated by filtration, washed with H_2O, and dried. The crystals were dissolved in CH_2Cl_2, the organic layer was washed with H_2O, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with hexane:CH_2Cl_2 (3:7) to give **11j** (16.8 g, quant.).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.60 (4H, d, $J_{H\text{-}F}$ = 48.0 Hz, C-2H), 6.53 (1H, s, C-3H), 7.03 (1H, d, J = 9.0 Hz, C-8H), 8.10–8.40 (2H, m, C-5H, C-7H); mp 142–143 °C (EtOH); MS (EI) m/z 266 (M^+); anal. ($C_{12}H_8F_2N_2O_2$) C, H, N.

6-Bromo-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carbonitrile (11b). A mixture of **11j** (4.2 g, 15.8 mmol), tin(II) chloride (9.6 g, 50.6 mmol), and EtOH (140 mL) was stirred for 2 h at 80 °C. After cooling down to room temperature, 2 N NaOH was added to the mixture and the mixture was extracted with CH_2Cl_2. The organic extracts were extracted with 2 N HCl. The aqueous acidic extracts were alkalinized with 2 N NaOH, and extracted with CH_2Cl_2. The extracts was washed with brine, dried (Na_2SO_4), and evaporated to give crude amine **11a** (2.4 g, 65%) as an oil, which was used without further purification.

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.57 (4H, d, J = 48.0 Hz, C-2H), 6.36 (1H, s, C-3H), 6.28–6.94 (3H, m, C-5H, C-7H, C-8H); MS (EI) m/z 236 (M^+).

An aqueous solution (10 mL) of sodium nitrite (760 mg, 11.0 mmol) was added to a mixture of the crude amine **11a** (2.0 g, 8.47 mmol) and concd H_2SO_4 (20 mL) dropwise with stirring at 0 °C. Stirring was continued for 30 min at 0 °C. The reaction mixture was added dropwise to a mixture of copper(I) bromide (2.43 g, 16.9 mmol) and 48% aqueous HBr (12 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, at room temperature for 1 h, and heated at 70 °C for 1 h. After cooling down to room temperature, the reaction mixture was extracted with CH_2Cl_2. The organic layer was washed with 2 N HCl, 2 N NaOH, and brine, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with hexane:AcOEt (5:1) to give **11b** (1.63 g, 64%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.55 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.41 (1H, s, C-3H), 6.75 (1H, d, J = 9.0 Hz, C-8H), 7.13–7.83 (2H, m, C-5H, C-7H); mp 105–107 °C (AcOEt:hexane); MS (EI) m/z 299 (M^+); anal. ($C_{12}H_8BrF_2NO$) C, H, N.

6-Bromo-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxylic acid (9b). A mixture of **11b** (1.53 g, 5.10 mmol), AcOH (30 mL), concd H_2SO_4 (15 mL), and H_2O (15 mL) was refluxed for 3 h. After cooling down to room temperature, the mixture was poured into ice–water, extracted with Et_2O. The organic extracts were washed with brine, water, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with hexane:AcOEt (2:1) to give **9b** (1.23 g, 76%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 4.58 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 6.77 (1H, d, J = 9.0 Hz, C-8H), 6.83 (1H, s, C-3H), 7.29 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.14 (1H, d, J = 2.0 Hz, C-5H), 9.81 (1H, br s); mp 165–166 °C (AcOEt:hexane); MS (EI) m/z 318 (M^+); anal. ($C_{12}H_9BrF_2O_3$) C, H, N.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-carboxamide (13j).** A mixture of **9j** (0.38 g, 1.33 mmol) and THF (5 mL) was cooled to 0 °C, 1,1′-carbonyldiimidazole (CDI) (0.28 g, 1.73 mmol) was added portionwise to the mixture. The mixture was stirred at 0 °C for 1 h, and then 2-cyanoethylamine (0.15 g, 2.14 mmol) in THF (2 mL) was added at 0 °C to the reaction mixture, and the mixture was stirred at 0 °C for 12 h. H_2O was added to the reaction mixture, and the products were extracted with CH_2Cl_2. The extracts were washed with brine, dried (Na_2SO_4), evaporated, and chromatographed on silica gel with MeOH:CH_2Cl_2 (5:100) to give **13j** (0.38 g, 85%).

60 MHz ^{1}H NMR ($CDCl_3$–DMSO-d_6, TMS) δ 2.69 (2H, t, J = 6.0 Hz, CH_2CN), 3.53 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.55 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 6.12 (1H, s, C-3H), 6.88 (1H, d, J = 9.0 Hz, C-8H), 7.97 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 8.43 (1H, d, J = 2.0 Hz, C-5H); mp 179–180 °C (EtOH); MS (EI) m/z 337 (M^+); anal. ($C_{15}H_{13}F_2N_3O_4$) C, H, N.

6-Bromo-2,2-bis(fluoromethyl)-*N*-methyl-2*H*-1-benzopyran-4-carboxamide (12b). 60 MHz ^{1}H NMR ($CDCl_3$–CD_3OD, TMS) δ 2.77 (3H, s, NHCH_3), 4.56 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 5.94 (1H, s, C-3H), 6.77 (1H, d, J = 9.0 Hz, C-8H), 7.31 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.63 (1H, d, J = 2.0 Hz, C-5H); mp 187–188 °C (AcOEt:hexane); MS (EI) m/z 331 (M^+); anal. ($C_{13}H_{12}BrF_2NO_2$) C, H, N; yield 88%.

6-Chloro-2,2-bis(fluoromethyl)-*N*-methyl-2*H*-1-benzopyran-4-carboxamide (12c). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.93 (3H, d, J = 5.0 Hz, NHCH_3), 4.56 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.88 (1H, br s, NH), 5.96 (1H, s, C-3H), 6.82 (1H, d, J = 9.0 Hz, C-8H), 7.21 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.54 (1H, d, J = 2.0 Hz, C-5H); mp 175–176 °C (AcOEt:hexane); MS (EI) m/z 287 (M^+); anal. ($C_{13}H_{12}ClF_2NO_2$) C, H, N; yield 29%.

2,2-Bis(fluoromethyl)-*N*-methyl-2*H*-1-benzopyran-4-carboxamide (12d). 60 MHz ^{1}H NMR ($CDCl_3$, TMS): δ 2.85 (3H, d, J = 5.0 Hz, NHCH_3), 4.49 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.86 (1H, s, C-3H), 6.11 (1H, br s, NH), 6.70–7.50 (4H, m, C-5H, C-6H, C-7H, C-8H); mp 138–139 °C (AcOEt:hexane); MS (EI) m/z 253 (M^+); anal. ($C_{13}H_{13}F_2NO_2$) C, H, N; yield 42%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-(trifluoromethyl)-2*H*-1-benzopyran-4-carboxamide (12e). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.88(3H, d, J = 5.0 Hz, NHCH_3), 4.53 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.99 (1H, s, C-3H), 6.48 (1H, br s, NH), 6.95 (1H, d, J = 9.0 Hz, C-8H), 7.48 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.82 (1H, d, J = 2.0 Hz, C-5H); mp 162–164 °C (AcOEt:hexane); MS (EI) m/z 321 (M^+); anal. ($C_{14}H_{12}F_5NO_2$) C, H, N; yield 86%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-(pentafluoroethyl)-2*H*-1-benzopyran-4-carboxamide (12f). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.87(3H, d, $J_{H\text{-}F}$ = 5.0 Hz, NHCH_3), 4.48 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 5.89 (1H, s, C-3H), 6.13 (1H, br s, NH), 6.87 (1H, d, J = 9.0 Hz, C-8H), 7.33 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.68 (1H, d, J = 2.0 Hz, C-5H); mp 128–129 °C (AcOEt:hexane); MS (EI) m/z 371 (M^+); anal. ($C_{15}H_{12}F_7NO_2$) C, H, N; yield 72%.

2,2-Bis(fluoromethyl)-6-(heptafluoropropyl)-*N*-methyl-2*H*-1-benzopyran-4-carboxamide (12g). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.94 (3H, d, J = 5.0 Hz, NHCH_3), 4.59 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.02 (1H, s, C-3H), 6.39 (1H, br s, NH), 7.01 (1H, d, J = 9.0 Hz, C-8H), 7.47 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.82 (1H, d, J = 2.0 Hz, C-5H); mp 88–91 °C (AcOEt:hexane); MS (EI) m/z 421 (M^+); anal. ($C_{16}H_{12}F_9NO_2$) C, H, N; yield 77%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-(nonafluorobutyl)-2*H*-1-benzopyran-4-carboxamide (12h). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.94 (3H, d, J = 5.0 Hz, NHCH_3), 4.56 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.92 (1H, br s, NH), 5.98 (1H, s, C-3H), 6.99 (1H, d, J = 9.0 Hz, C-8H), 7.45 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.78 (1H, d, J = 2.0 Hz, C-5H); MS (EI) m/z 471 (M^+). Analysis by HPLC (solvent, CH_3CN:H_2O:TFA = 64.95:34.95:0.1; flow rate, 1.0 cm^3/min; detection, 254 nm) showed the purity to be at least 96% (retention time 11 min), and (solvent, CH_3OH:H_2O:TFA = 74.95:24.95:0.1; flow rate, 1.0 cm^3/min; detection, 254 nm) showed the purity to be at least 97% (retention time 16 min); yield 63%; colorless oil.

6-Cyano-2,2-bis(fluoromethyl)-*N*-methyl-2*H*-1-benzopyran-4-carboxamide (12i). 270 MHz ^{1}H NMR (DMSO-d_6, TMS) δ 2.74 (3H, d, J = 4.62 Hz, NHCH_3), 4.65 (4H, d, $J_{H\text{-}F}$ = 47.8 Hz, C-2H), 6.13 (1H, s, C-3H), 7.07 (1H, d, J = 8.57 Hz, C-8H), 7.68 (1H, dd, J = 8.57, 1.98 Hz, C-7H), 7.87 (1H, d, J = 1.98 Hz, C-5H), 8.48 (1H, d, J = 4.62 Hz, NH); mp 206–207 °C (AcOEt:hexane); MS (EI) m/z 278 (M^+); anal. ($C_{14}H_{12}F_2N_2O_4$) C, H, N; yield 95%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-nitro-2*H*-1-benzopyran-4-carboxamide (12j). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.80 (3H, d, J = 4.5 Hz, NHCH_3), 4.68 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.21 (1H, s, C-3H), 7.08 (1H, d, J = 9.0 Hz, C-8H), 8.10 (1H, dd, J = 9.0, 3.0 Hz, C-7H), 8.46 (1H, br s, NH), 8.48 (1H, d, J = 3.0 Hz, C-5H); mp 180–181 °C (AcOEt:hexane); MS (EI) m/z 298 (M^+); anal. ($C_{13}H_{12}F_2N_2O_4$) C, H, N; yield 67%.

6-Bromo-*N*-cyanoethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxamide (13b). 60 MHz ^{1}H NMR ($CDCl_3$–CD_3OD, TMS) δ 2.75 (2H, t, J = 6.0 Hz, CH_2CN), 3.63 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.61 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.04 (1H, s, C-3H), 6.81 (1H, d, J = 9.0 Hz, C-8H), 7.36 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.69 (1H, d, J = 2.0 Hz, C-5H); mp 140–142 °C (AcOEt:hexane); MS (EI) m/z 370 (M^+); anal. ($C_{15}H_{13}BrF_2NO_2$) C, H, N; yield 81%.

6-Chloro-*N*-cyanoethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxamide (13c). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.72 (2H, t, J = 6.0 Hz, CH_2CN), 3.64 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.54 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.01 (1H, s, C-3H), 6.57 (1H, br s, NH), 6.82 (1H, d, J = 9.0 Hz, C-8H), 7.18 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.51 (1H, d, J = 2.0 Hz, C-5H); mp 134–136 °C (AcOEt:hexane); MS (EI) m/z 326 (M^+); anal. ($C_{15}H_{12}ClF_2N_2O_2$) C, H, N; yield 39%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxamide (13d).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.71 (2H, t, J = 6.0 Hz, CH_2CN), 3.62 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.57 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.99 (1H, s, C-3H), 6.20–7.60 (5H, m, C-5H, C-6H, C-7H, C-8H, NH). MS m/z: 292 (M^+). Analysis by HPLC (solvent, CH_3CN:H_2O:TFA = 34.95:64.95:0.1; flow rate, 1.0 cm^3/min; detection, 254 nm) showed the purity to be at least 96% (retention time 14 min), and (solvent, MeOH:H_2O:TFA = 44.95:54.95:0.1; flow rate, 1.0 cm^3/min; detection, 254 nm) showed the purity to be at least 95% (retention time 14 min); yield 51%; colorless oil.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(trifluoromethyl)-2*H*-1-benzopyran-4-carboxamide (13e).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.70 (2H, t, J = 6.0 Hz, CH_2CN), 3.63 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.57 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.07 (1H, s, C-3H), 6.96 (1H, br s, NH). 6.98 (1H, d, J = 9.0 Hz, C-8H), 7.50 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.84 (1H, d, J = 2.0 Hz, C-5H); mp 135–136 °C (AcOEt:hexane); MS (EI) m/z: 360 (M^+); anal. ($C_{16}H_{13}F_5N_2O_2$) C, H, N; yield 86%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(pentafluoroethyl)-2*H*-1-benzopyran-4-carboxamide (13f).** 270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.75 (2H, t, J = 6.27 Hz, CH_2CN), 3.67 (2H, dt, J = 6.27, 6.27 Hz, NHCH_2), 4.59 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.08 (1H, s, C-3H), 6.80 (1H, br s, NH), 7.02 (1H, d, J = 9.0 Hz, C-8H), 7.52 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.83 (1H, d, J = 2.0 Hz, C-5H); mp 144–145 °C (AcOEt:hexane); MS (EI) m/z: 410 (M^+); anal. ($C_{17}H_{13}F_9N_2O_2$) C, H, N; yield 83%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(heptafluoropropyl)-2*H*-1-benzopyran-4-carboxamide (13g).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS): δ 2.70 (2H, t, J = 6.0 Hz, CH_2 CN), 3.62 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.58 (4H,

d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 6.05 (1H, s, C-3H), 6.51 (1H, br s, NH), 7.03 (1H, d, J = 8.58 Hz, C-8H), 7.43 (1H, dd, J = 8.58, 1.98 Hz, C-7H), 7.81 (1H, d, J = 1.98 Hz, C-5H); mp 135–136 °C (AcOEt:hexane); MS (EI) m/z 460 (M^+); anal. ($C_{18}H_{13}F_9N_2O_2$) C, H, N; yield 45%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(nonafluorobutyl)-2*H*-1-benzopyran-4-carboxamide (13h).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.69 (2H, t, J = 6.0 Hz, CH_2 CN), 3.60 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.55 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 6.08 (1H, s, C-3H), 6.83 (1H, br s, NH), 6.99 (1H, d, J = 9.0 Hz, C-8H), 7.47 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.81 (1H, d, J = 2.0 Hz, C-5H); mp 85–86 °C (Et_2O:hexane); MS (EI) m/z 510 (M^+); anal. ($C_{19}H_{13}F_{11}N_2O_2$) C, H, N; yield 63%.

6-Cyano-*N*-cyanoethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-carboxamide (13i). 270 MHz ^{1}H NMR (DMSO-d_6, TMS) δ 2.79 (2H, t, J = 6.27 Hz, CH_2CN), 3.47 (2H, dt, J = 6.27, 6.54 Hz, NHCH_2), 4.68 (4H, d, $J_{H\text{-}F}$ = 47.8 Hz, C-2H), 6.15 (1H, s, C-3H), 7.09 (1H, d, J = 8.57 Hz, C-8H), 7.70 (1H, dd, J = 8.57, 1.98 Hz, C-7H), 7.78 (1H, d, J = 1.98 Hz, C-5H), 8.91 (1H, br s, NH); mp 170–172 °C (AcOEt:hexane). MS (EI) m/z 317 (M^+); anal. ($C_{16}H_{13}F_2N_3O_2$) C, H, N; yield 72%.

6-Amino-*N*-cyanoethyl-2,2-bis(fluoromethyl)-*N*-methyl-2*H*-1-benzopyran-4-carboxamide hydrochloride (13a). A mixture of **13j** (0.51 g, 1.5 mmol), $SnCl_2$ (0.99 g, 4.7 mmol), and EtOH (3 mL) was refluxed for 2.5 h. After cooling down to room temperature, 2 N NaOH was added to the mixture, and the products were extracted with CH_2Cl_2. The extracts were washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel with AcOEt:hexane (1:1) to give amine. A mixture of the obtained amine, MeOH, and concd HCl was stirred for 1 h at ambient temperature. The reaction mixture was evaporated under vacuum to give **13a** (0.35 g, 67%).

270 MHz ^{1}H NMR (DMSO-d_6, TMS) δ 2.77 (2H, t, J = 6.27 Hz, CH_2CN), 3.45 (2H, dt, J = 6.27, 6.27 Hz, NHCH_2), 4.64 (4H, d, $J_{H\text{-}F}$ = 47.8 Hz, C-2H), 6.11 (1H, s, C-3H), 7.00 (1H, d, J = 8.58 Hz, C-8H), 7.16–7.23 (1H, m, C-7H), 7.51–7.55 (1H, m, C-5H), 9.3–10.2 (1H, br s, NH); mp 202–205 °C (AcOEt:EtOH); MS (EI) m/z 307 (M^+); anal. ($C_{15}H_{16}ClF_2N_3O_2{\cdot}1/4H_2O$) C, H, N.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-nitro-2*H*-1-benzopyran-4-thioamide (15j).** A mixture of **13j** (25.9 g, 76.6 mmol), Lawesson's reagent (95%) (16.3 g, 38.3 mmol), and 1,2-dichloroethane (520 mL) was refluxed for 1 h. After cooling down to room temperature, the reaction mixture was washed with 1 N NaOH and aqueous layer was extracted with AcOEt. The 1,2-dichloroethane and AcOEt layer was washed with brine, and dried (Na_2SO_4), evaporated, and chromatographed on silica gel with AcOEt:hexane (1:3) to give **15j** (25.5 g, 94%).

60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.91 (2H, t, J = 6.0 Hz, CH_2CN), 4.02 (2H, dt, J = 6.0, 6.0 Hz NHCH_2), 4.58 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 5.86 (1H, s, C-3H), 6.95 (1H, d, J = 9.0 Hz, C-8H), 8.04 (1H, dd, J = 9.0, 3.0 Hz, C-7H), 8.32 (1H, d, J = 3.0 Hz, C-5H), 8.37 (1H, br s, NH); mp 156–157 °C (AcOEt); MS (EI) m/z 353 (M^+); anal. ($C_{15}H_{13}F_2N_3O_2S$) C, H, N.

2,2-Bis(fluoromethyl)-*N*-methyl-6-(trifluoromethyl)-2*H*-1-benzopyran-4-thioamide (14e). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 3.25 (3H, d, J = 5.0 Hz, NCH_3), 4.54 (1H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 5.77 (1H, s, C-3H), 6.93 (1H, d, J = 9.0 Hz, C-8H), 7.44 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.54 (1H, br s, NH), 7.66 (1H, d, J = 2.0 Hz, C-5H); mp 145–147 °C (AcOEt:hexane); MS (EI) m/z 337 (M^+); anal. ($C_{14}H_{12}F_5NOS$) C, H, N; yield 50%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-(pentafluoroethyl)-2*H*-1-benzopyran-4-thioamide (14f). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 3.27 (3H, d, J = 5.0 Hz, NCH_3), 4.55 (4H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 5.80 (1H, s, C-3H), 6.97 (1H, d, J = 9.0 Hz, C-8H), 7.40 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.55 (1H, br s, NH), 7.63 (1H, d, J = 2.0 Hz, C-5H); mp 148–149 °C (AcOEt:hexane); MS (EI) m/z 387 (M^+); anal. ($C_{15}H_{12}F_7NOS$) C, H, N; yield 96%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-(heptafluoropropyl)-2*H*-1-benzopyran-4-thioamide (14g). 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 3.24 (3H, d, J = 5.0 Hz, NCH_3), 4.55 (1H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.82 (1H, s, C-3H), 6.98 (1H, d, J = 9.0 Hz, C-8H), 7.42 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.55 (1H, br s, NH), 7.62 (1H, d, J = 2.0 Hz, C-5H); mp 125–126 °C (Et_2O:hexane); MS (EI) m/z 437 (M^+); anal. ($C_{16}H_{12}F_9NOS$) C, H, N; yield 96%.

6-Cyano-2,2-bis(fluoromethyl)-*N*-methyl-2*H*-1-benzopyran-4-thioamide (14i). 270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 3.26 (3H, d, J = 4.88 Hz, NCH_3), 4.58 (1H, $J_{H\text{-}F}$ = 46.9 Hz, C-2H), 5.80 (1H, s, C-3H), 6.95 (1H, d, J = 8.55 Hz, C-8H), 7.45 (1H, dd, J = 8.55, 1.95 Hz, C-7H), 7.77 (1H, d, J = 1.95 Hz, C-5H), 8.10 (1H, br s, NH); mp 137–138 °C (Et_2O:hexane); MS (EI) m/z: 294 (M^+); anal. ($C_{14}H_{12}F_2N_2OS$) C, H, N; yield 50%.

2,2-Bis(fluoromethyl)-*N*-methyl-6-nitro-2*H*-1-benzopyran-4-thioamide (14j). 60 MHz ^{1}H NMR ($CDCl_3$–DMSO-d_6, TMS) δ 3.14 (3H, s, NCH_3), 4.51 (1H, d, $J_{H\text{-}F}$ = 46.0 Hz, C-2H), 5.70 (1H, s, C-3H), 6.85 (1H, d, J = 9.0 Hz, C-8H), 7.91 (1H, dd, J = 9.0, 3.0 Hz, C-7H), 8.22 (1H, d, J = 3.0 Hz, C-5H); mp 135–136 °C (AcOEt:hexane); MS (EI) m/z 314 (M^+); anal. ($C_{13}H_{12}F_2N_2O_3S$) C, H, N; yield 96%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(trifluoromethyl)-2*H*-1-benzopyran-4-thioamide (15e).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.89 (2H, t, J = 6.0 Hz, CH_2CN), 4.03 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.60 (4H, d, $J_{H\text{-}F}$ = 47.0 Hz, C-2H), 5.87 (1H, s, C-3H), 7.02 (1H, d, J = 9.0 Hz, C-8H), 7.51 (1H, dd, J = 9.0, 2.0 Hz, C-7H), 7.82 (1H, d, J = 2.0 Hz, C-5H), 8.35 (1H, br s, NH); mp 105–106 °C (AcOEt:hexane); MS (EI) m/z 376 (M^+); anal. ($C_{16}H_{13}F_5N_2OS$) C, H, N; yield 52%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(pentafluoroethyl)-2*H*-1-benzopyran-4-thioamide (15f).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.89 (2H, t, J = 6.0 Hz, CH_2CN), 4.04 (2H, dt, J = 6.0, 6.0 Hz, NHCH_2), 4.57 (4H, d, $J_{H\text{-}F}$ =

47.0 Hz, C-2H), 5.84 (1H, s, C-3H), 7.00 (1H, d, $J=9.0$ Hz, C-8H), 7.46 (1H, dd, $J=9.0$, 2.0 Hz, C-7H), 7.64 (1H, d, $J=2.0$ Hz, C-5H), 7.98–8.40 (1H, br s, NH); mp 108–109 °C (AcOEt:hexane); MS (EI) m/z: 426 (M^+); anal. ($C_{17}H_{13}F_7N_2OS$) C, H, N; yield 62%.

***N*-Cyanoethyl-2,2-bis(fluoromethyl)-6-(heptafluoropropyl)-2*H*-1-benzopyran-4-thioamide (15g).** 60 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.85 (2H, t, $J=6.0$ Hz, CH_2CN), 3.95 (2H, dt, $J=6.0$, 6.0 Hz, $NHCH_2$), 4.51 (4H, d, $J_{H\text{-}F}=47.0$ Hz, C-2H), 5.78 (1H, s, C-3H), 6.92 (1H, d, $J=9.0$ Hz, C-8H), 7.37 (1H, dd, $J=9.0$, 2.0 Hz, C-7H), 7.56 (1H, d, $J=2.0$ Hz, C-5H), 8.20 (1H, br s, NH); mp 94–95 °C (AcOEt:hexane); MS (EI) m/z: 476 (M^+); anal. ($C_{18}H_{13}F_9N_2OS$) C, H, N; yield 44%.

6-Cyano-*N*-cyanoethyl-2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-thioamide (15i). 270 MHz ^{1}H NMR ($CDCl_3$, TMS) δ 2.96 (2H, t, $J=6.27$ Hz, CH_2CN), 4.05 (2H, dt, $J=6.27$, 6.27 Hz, $NHCH_2$), 4.60 (4H, d, $J_{H\text{-}F}=47.0$ Hz, C-2H), 5.87 (1H, s, C-3H), 6.98 (1H, d, $J=8.54$ Hz, C-8H), 7.47 (1H, dd, $J=8.54$, 1.96 Hz, C-7H), 7.78 (1H, d, $J=1.96$ Hz, C-5H), 8.30 (1H, br s, NH); mp 191–192 °C (AcOEt:hexane); MS m/z: 333 (M^+); anal. ($C_{16}H_{13}F_2N_3OS$) C, H, N; yield 55%.

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