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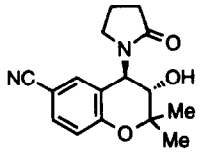
VASORELAXANT ACTIVITY OF 2-FLUOROMETHYLBENZOPYRAN K^+ CHANNEL OPENERS

Naoki Taka, Hiroshi Koga,* Haruhiko Sato, Takenori Ishizawa, Tadakatsu Takahashi, and Jun-ichi Imagawa

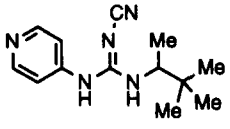
Fuji-gotemba Research Laboratories, Chugai Pharmaceutical Co., Ltd., 1-135, Komakado, Gotemba, Shizuoka, 412, Japan

Abstract: Synthesis and vasorelaxant activity of 2-fluoromethylbenzopyrans are explained. These 2-fluoromethyl derivatives showed a potent smooth muscle relaxant activity.

K^+ channel openers such as cromakalim (**1**), pinacidil (**2**), and RP49356 (**3**), have been reported to increase K^+ conductance of smooth muscle membrane, resulting in hyperpolarization of resting potential and relaxation of smooth muscles. These K^+ channel openers have a potential value in the treatment of diseases involving smooth muscle contraction, such as asthma, hypertension, and urinary incontinence.[1] Cromakalim (**1**) is a prototype of benzopyran K^+ channel openers.[1] Recently, numerous benzopyran K^+ channel openers have appeared. These include emakalim (**4**), bimakalim (**5**), and Ro31-6930 (**6**).[1] These benzopyrans have a 2,2-dimethyl group in common, but little is known about the 2-fluoromethyl analogues.



Cromakalim (**1**)



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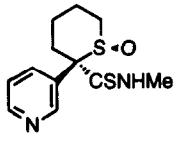
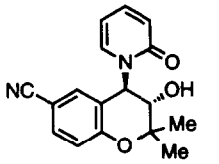
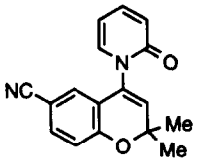


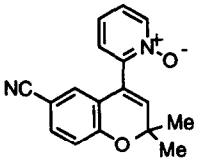
RP49356 (**3**)



Emakalim (**4**)



Bimakalim (**5**)



Ro 31-6930 (**6**)

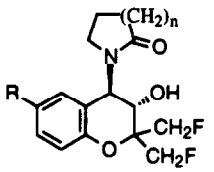
In the course of our studies to find more promising K^+ channel openers,[2] we investigated the synthesis of 2-fluoromethylbenzopyran derivatives. In this paper, we wish to report the synthesis and biological activity of 2-fluoromethylbenzopyrans .

The compounds prepared in this study are listed in Tables I and II, and their synthetic routes are outlined in Schemes I and II. The starting materials were the epoxides **8**, which were prepared from benzopyrans **7** by treatment with *m*-chloroperbenzoic acid (*m*-CPBA). The 6-cyano derivative **7a** was prepared from the 6-nitro derivative **7b**[2f] through the 6-iodo derivative **7d** in moderate yield. The 6-pentafluoroethyl derivative **7c** was prepared from **7d** by the usual way.[3] The epoxides **8** were treated with cyclic amide and base (NaH or KO-*t*-Bu) to afford the mixture of *trans*-4-(cyclic amido)-3,4-dihydro-2*H*-1-benzopyran-3-ols **9** (or **11**) and 4-(cyclic amido)-benzopyrans **10** (or **12**) (Method A)(Scheme I). The epoxides **8** were also heated with 2-hydroxypyridine in pyridine to give the *trans*-4-(1,2-dihydro-2-oxo-1-pyridyl)-3,4-dihydro-2*H*-1-benzopyran-3-ols **13** as main products. The 3,4-dihydrobenzopyran-3-ol derivatives **9**, **11**, and **13** were converted to the corresponding dehydrated compounds **10**, **12**, and **14** by treatment with methanesulfonyl chloride and triethylamine, followed by treatment with sodium hydride (Method B), or with sodium hydroxide-carrier in dioxane (Method C). The synthesis of the 2-[2,2-bis(fluoromethyl)-2*H*-1-benzopyran-4-yl]pyridine *N*-oxide derivatives **17** are shown in Scheme II. The known 3,4-dihydro-6-nitro-4-oxobenzopyran **15b**[2f] was treated with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 4-dimethylaminopyridine (DMAP) and the resulting 2,2-bis(fluoromethyl)-6-nitro-4-trifluoromethanesulfonyloxy-2*H*-1-benzopyran was allowed to react with 2-trimethylstannylpyridine in the presence of $Pd_2(dba)_3(CHCl_3)$ as the catalyst to afford 6-nitro-4-(2-pyridyl)benzopyran **16b**.[4] The 6-cyano analogue **16a** was also prepared from the 4-oxo derivative **15a** by the similar way. The 6-pentafluoroethyl derivative **16c** was obtained from the 6-nitro compound **16b** by the same procedure as the synthesis of **7c**. The 4-(2-pyridyl)benzopyrans **16** were then treated with *m*-CPBA to afford the *N*-oxide derivatives **17**.

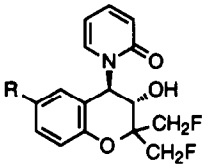
The vasorelaxant activities of compounds were determined by the effects on 30 mM KCl responses in rat isolated aorta and are shown in Tables I and II in comparison with cromakalim (**1**),[5] pinacidil (**2**),[6] RP49356 (**3**),[7] bimakalim (**5**),[8] and Ro 31-6930 (**6**).[9]

The 2-fluoromethyl compounds possessed vasorelaxant activities almost comparable to or slightly more potent than the corresponding 2-methyl analogues. Regarding other substituents, the effect of the 3-hydroxyl group appeared to vary with the 4-substituent, when compared to the corresponding dehydrated compounds. Among the 3-hydroxyl compounds, the piperidone group is a favored one as the 4-substituent. On the other hand, for the dehydrated form, the pyridone and pyridine *N*-oxide groups seem to be more attractive. The 6-nitro and pentafluoroethyl groups were generally superior to the 6-cyano group and the pentafluoroethyl group occasionally most favorable. Some of these 2-fluoromethyl compounds possess potent and long-lasting activity *in vivo*.[2f, 10]

Table I. Pysical Property and Vasorelaxant Activity of 2,2-Bis(fluoromethyl)-3,4-dihydrobenzopyran-3-ols



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



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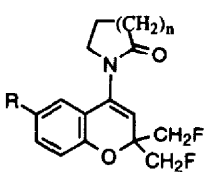
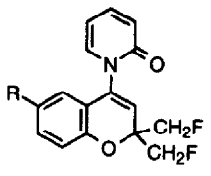
Compd.	R	% yield[a]	mp, ℃	rat aorta pEC$_{50}$[b]	rat aorta IA (%)[c]	n[d]
9a	CN	12	216-218	7.07±0.08	78.0±8.1	3
9b	NO_2	16	256-258	7.62±0.10	72.7±2.9	3
9c	C_2F_5	48	196-197	8.20±0.02	77.6±4.2	3
11a	CN	59	201-203	8.05±0.03	74.9±4.7	3
11b	NO_2	3	231-233	8.56±0.01	63.3±2.6	3
11c	C_2F_5	63	199-200	8.41±0.10	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	C_2F_5	56	162-164	7.92±0.14	82.8±3.6	3
cromakalim (**1**)				6.77±0.03	74.7±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. See reference 2a for experimental details. [c]Intrinsic activity ± SEM (%). [d]Number of determinations.

Table II. Physical Property and Vasorelaxnt Activity of 2,2-Bis(fluoromethyl)benzopyrans



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



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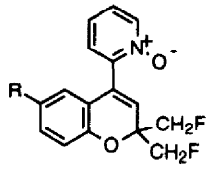
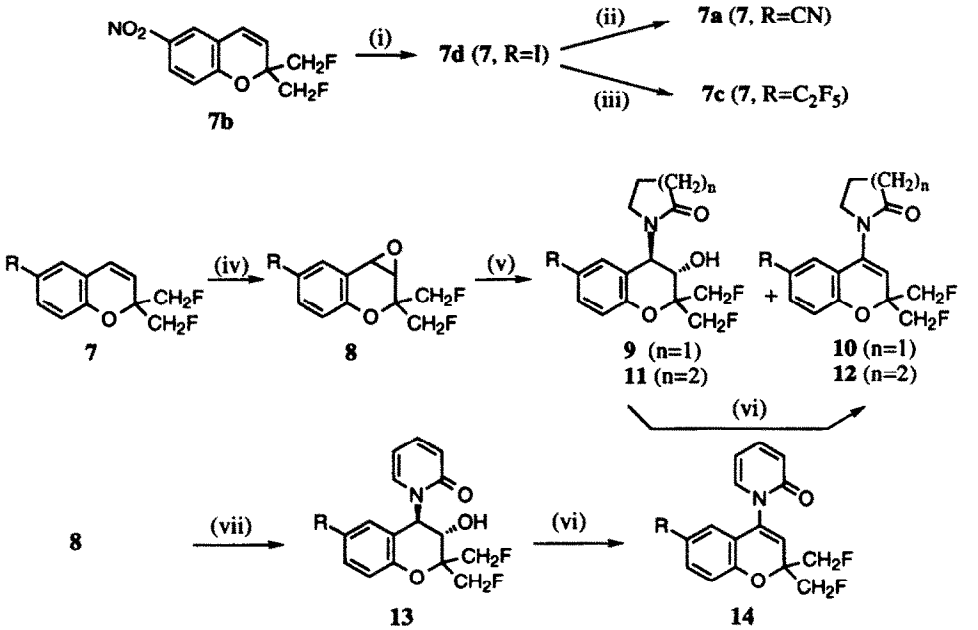


17

Compd.	R	method	% yield[a]	mp, ℃	rat aorta pEC$_{50}$[b]	rat aorta IA (%)[c]	n[d]
10a	CN	A	29	140-141	6.99±0.07	74.4±4.8	3
10b	NO_2	A	20	147-148	8.11±0.09	74.3±1.1	3
10c	C_2F_5	A	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	C_2F_5	A	3	149-150	8.25±0.08	72.0±5.4	3
		B	87				
		C	75				
14a	CN	C	54	174-175	7.61±0.07	75.7±1.6	3
14b	NO_2	C	74	171-173	8.61±0.01	64.9±4.1	3
14c	C_2F_5	B	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		85	183-184	8.76±0.02	66.3±1.1	3
17c	C_2F_5		8	105-107	8.77±0.16	68.2±4.1	3
cromakalim (**1**)					6.77±0.03	74.7±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

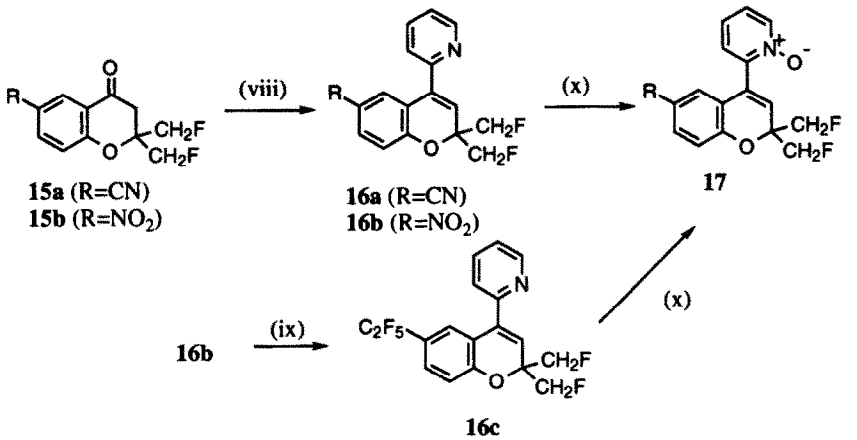
[a]Satisfactory microanalysis was obtained for all crystalline compounds. [b]Negative logarithm of the molar concentration required to relax rat aorta precontracted with 30 mM KCl by 50% of IA, with ± SEM. See reference 2a for experimental details. [c]Intrinsic activity ± SEM (%). [d]Number of determinations.

Scheme I



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

Scheme II



(viii) a) Tf_2O, DMAP, CH_2Cl_2 (39-97%) b) 2-trimethylstannylpyridine, $Pd_2(dba)_3(CHCl_3)$, PPh_3, LiCl, THF (83%) (ix) a) $SnCl_2$, EtOH b) $NaNO_2$, conc. H_2SO_4, KI, CH_2Cl_2 (63% from **16b**) c) C_2F_5COOK, CuI, toluene, DMF (70%) (x) *m*-CPBA, CH_2Cl_2

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