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VASORELAXANT ACTIVITY OF 2-FLUOROALKYL-6-NITRO-2*H*-1-BENZOPYRAN-4-CARBOTHIOAMIDE AND -CARBOXAMIDE K+ CHANNEL OPENERS

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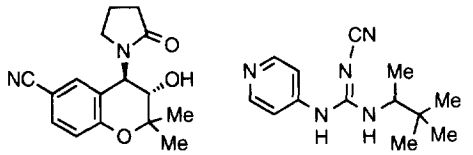
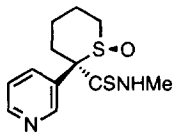
Abstract: Synthesis and vasorelaxant activity of 2-fluoroalkyl-6-nitro-2*H*-1-benzopyran-4-carbothioamides **4** and **6** and -carboxamides **5** and **7** are described. Potent smooth muscle relaxant activity was displayed by **6c**.

K^+ channel openers show the function of vasorelaxation through hyperpolarization of the cell membrane in smooth muscle. These drugs have attracted considerable attention because of their therapeutic potential in the treatment of those disorders in which smooth muscle contraction is involved. Particular applications include asthma, hypertension, and urinary incontinence.[1] Several compounds such as cromakalim (**1**), pinacidil (**2**), and RP49356 (**3**) have been identified as K^+ channel openers , and they possess specific affinity for ATP-sensitive K^+ channel.[1]

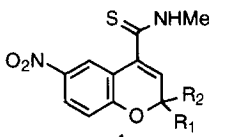


Cromakalim (**1**)

Pinacidil (**2**)



RP49356 (**3**)



4

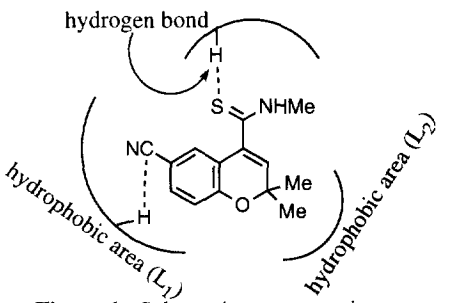


Figure 1. Schematic representation of proposed pharmacophore model of K^+ channel openers

Previously, we constructed a pharmacophore model that rationalizes the structure-activity relationships of a chemically diverse and structurally unrelated group of K^+ channel openers **1**-**3**.[2a] The pharmacophore model proposed that the 2-substituent of benzopyran type K^+ channel openers interacts

hydrophobically with the receptor (Figure 1).[2a] To obtain further information for the structural requirements for K^+ channel openers, we have investigated the structure-activity relationships of the 2-substituent of 6-nitro-2*H*-1-benzopyran-4-carbothioamides **4**, and found that 2,2-spirocyclobutyl and 2,2-spirocyclopentyl derivatives possessed very potent vasorelaxant activities (pEC_{50} = 10.68 and 10.60, respectively).[2b] They were potent i.v. antihypertensives as expected, but they showed poor hypotensive activities when administered orally.[2c] In the course of our study to find compound **4** with increased p.o. antihypertensive activity, we knew that the 2-fluoroalkyl derivatives exhibited more favorable *in vitro* and *in vivo* (p.o.) vasorelaxant activities compared to the corresponding alkyl derivatives. In this paper, we wish to report the synthesis, *in vitro* vasorelaxant activity, and structure-activity relationships (SAR) of 2-fluoroalkyl-6-nitro-2*H*-1-benzopyran-4-carbothioamides **4** and **6** and -carboxamides **5** and **7.**

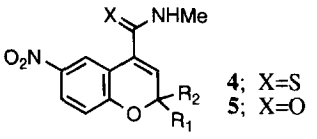
Compounds prepared in this study are listed in Table I, and their synthetic routes are outlined in Schemes I and II. The starting materials were the benzopyranes **10**, which were prepared from 6'-hydroxy-3'-nitroacetophenone (**8**) through ketones **9** by the usual way.[3] The benzopyranes **10** were brominated and subsequently treated with sodium hydroxide to afford the 4-bromo derivatives **11**. Compounds **11** were heated with cuprous cyanide to give the 4-cyano derivatives **12** that were smoothly hydrolyzed to result the carboxylic acids **13**. The acids **13** were readily converted to the amides **5** and **7** by treatment with amine in the presence of carbonyl diimidazole (CDI) (method A), or with thionyl chloride followed by addition of amine (method B). The thioamides **4** and **6** were obtained by treating the corresponding amide **5** and **7** with Lawesson's reagent (method C).

Owing to the inability of the above method to obtain the 2,2-bis(trifluoromethyl) derivatives,[4] a different synthetic route was used to prepare this type of compounds (Scheme II). Thus, condensation of the acetophenone **14** with hexafluoroacetone trihydrate in the presence of pyrrolidine in benzene provided the ketone **15** (mp 109-110 ℃, 29%). Compound **15** was treated with phosphoryl bromide to afford **16** (mp 93-94 ℃, 52%). Compound **16** was converted under Heck reaction to the acid **13e** (mp 96-97 ℃, 87%).[5] The amides **5e** and **7e** and thioamides **4e** and **6e** were obtained from the acid **13e** by the same procedure as described above.

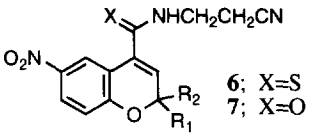
The vasorelaxant activities of compounds were determined by the effects on 30 mM KCl responses in rat isolated aorta and are shown in Table I in comparison with cromakalim (**1**),[6] pinacidil (**2**),[7] and RP49356 (**3**).[8]

The 2-fluoroalkyl derivatives possessed vasorelaxant activity comparable to or more potent than the corresponding 2,2-dimethyl analogs. The activity appeared to increase with the number of fluorine atom. This seems to imply that introduction of fluorine into the 2-methyl group increases the hydrophobic interaction at L2 site of the pharmacophore model (Figure 1)[2a], enhancing the activity. Among them, the most potent 2,2-bis(fluoromethyl) derivative **6c** (KC-399) was found to be some 1000-fold more potent than the reference compounds **1-3**. KC-399 (**6c**) showed a highly potent, slow and long-lasting antihypertensive effect with little reflex tachycardia.[9a]

Table I. Physical Properties and Vasorelaxant Activity of 6-Nitrobenzopyran-4-carbothioamides (**4** and **6**) and -carboxamides (**5** and **7**)



4; X=S
5; X=O

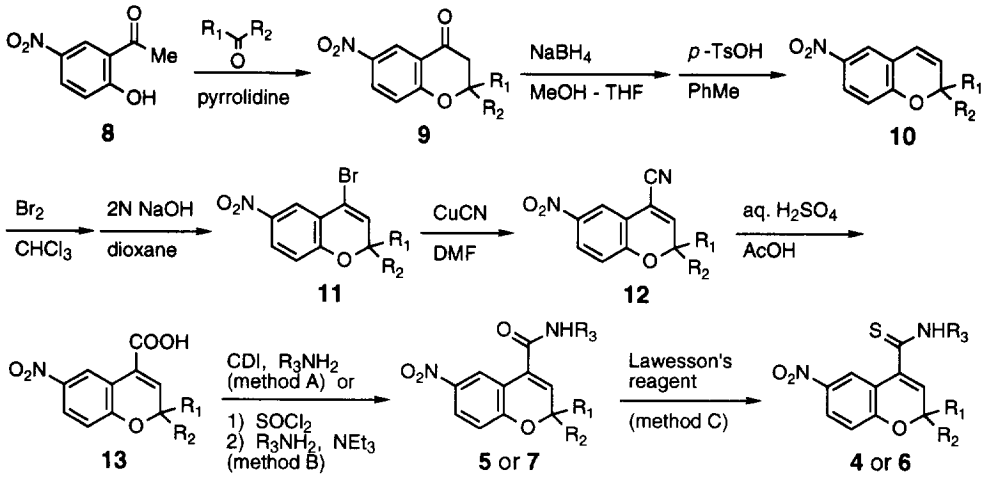


6; X=S
7; X=O

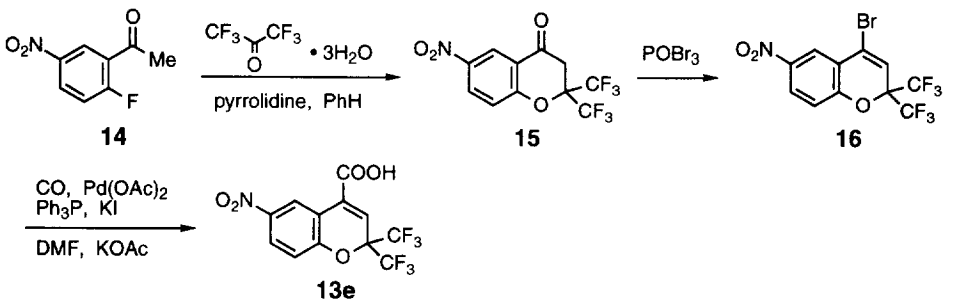
Compd.	R_1	R_2	X	method	% yield[a]	mp, ℃	rat aorta pEC_{50}[b]	rat aorta IA (%)[c]	rat aorta n[d]
4a[e]	Me	Me	S				8.87±0.05	63.5±4.7	5
5a[f]	Me	Me	O				7.97±0.04	61.0±5.1	4
6a	Me	Me	S	C	95	116-118	9.43±0.28	78.5±8.4	3
7a[f]	Me	Me	O				8.55±0.11	73.1±1.2	4
4b	Me	CH_2F	S	C	85	141-144	8.79±0.36	77.1±1.4	3
5b	Me	CH_2F	O	A	86	171-173	8.05±0.10	66.0±3.5	3
6b	Me	CH_2F	S	C	43	128-130	8.73±0.04	59.6±3.6	3
7b	Me	CH_2F	O	B	89	165-167	8.40±0.04	71.0±0.4	3
4c	CH_2F	CH_2F	S	C	96	135-136	9.32±0.11	74.5±8.9	3
5c	CH_2F	CH_2F	O	A	67	180-181	8.29±0.03	70.7±5.5	3
6c[g]	CH_2F	CH_2F	S				9.85±0.24	72.5±3.7	7
7c[g]	CH_2F	CH_2F	O				8.65±0.03	72.3±8.7	3
4d	Me	CF_3	S	C	86	158-160	9.52±0.34	62.5±7.6	3
5d	Me	CF_3	O	A	65	196-197	8.57±0.08	61.7±8.3	3
6d	Me	CF_3	S	C	50	149-150	9.44±0.11	69.7±7.3	3
7d	Me	CF_3	O	A	77	191-193	9.16±0.02	70.6±6.3	3
4e	CF_3	CF_3	S	C	92	161-162	9.20±0.02	68.0±4.6	3
5e	CF_3	CF_3	O	A	42	186-187	8.83±0.09	57.9±5.4	3
6e	CF_3	CF_3	S	C	57	131-132	9.36±0.13	74.8±3.0	3
7e	CF_3	CF_3	O	A	70	203-204	9.31±0.03	64.1±4.8	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. [e]See reference 9b. [f]See reference 9c. [g]See reference 9a.

Scheme I



Scheme II



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