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# VASORELAXANT ACTIVITY OF 2-SUBSTITUTED 6-NITRO-2*H*-1-BENZOPYRAN-4-CARBOTHIOAMIDE K+ CHANNEL OPENERS

Haruhiko Sato,* Hiroshi Koga,* Takenori Ishizawa, Toshihiko Makino, Kiyonori Kuromaru, Naoki Taka, Tadakatsu Takahashi, Tsutomu Sato, and Hiroyuki Nabata

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

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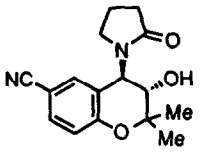
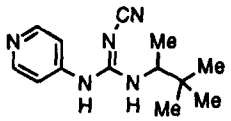
**Abstract:** Synthesis and vasorelaxant activity of 2-substituted 6-nitro-2*H*-1-benzopyran-4-carbothioamides **5** are described. Potent smooth muscle relaxant activity was displayed by **5c**, **5h**, and **5i**.

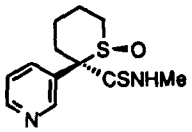
$K^+$ channel openers such as cromakalim (**1**), pinacidil (**2**), and RP49356 (**3**), have attracted considerable attention over the past few years because of evidence for their potential value in the treatment of those disorders in which smooth muscle contraction is involved.[1] Particular applications include asthma, hypertension, and urinary incontinence.[1]



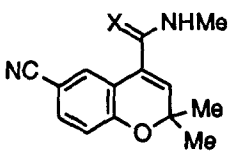

Cromakalim (**1**)



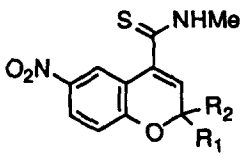

Pinacidil (**2**)




RP49356 (**3**)




**4**




**5**

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] We also designed new benzopyran $K^+$ channel openers **4** (X=S, O, NCN) using this model. These compounds were found to have potent smooth muscle relaxant activity, among which thioamide derivative **4** (X=S) was the most potent.[2a] The pharmacophore model also proposed that the 2-substituent of benzopyrans **4** interacts hydrophobically with the receptor.[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 benzopyrans **4**. Since the study on the 6-substituent of **4** (X=S) exhibited that the nitro group is the most favored,[2b] 6-nitro-2*H*-1-benzopyran-4-carbothioamides **5** were employed as the basic structure. In this paper, we wish to report the synthesis, biological activity, and structure-activity relationships of 2-substituted 6-nitro-2*H*-1-benzopyran-4-carbothioamides **5**.

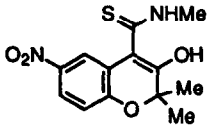
The compounds prepared in this study are listed in Table I, and their synthetic routes are outlined in Scheme I. The starting materials were the epoxides **6**, which were prepared from 6'-hydroxy-3'-nitroacetophenone in the usual way.[3] The epoxides **6** were rearranged to the ketones **7** by heating with *p*-toluenesulfonic acid (*p*-TsOH) in toluene. The treatment of the enolates derived from the ketones **7** with methylisothiocyanate gave the β-keto thioamides **8**. Reduction of **8** with sodium borohydride in MeOH gave the β-hydroxy thioamides **9** as a mixture of cis and trans isomers which could be readily separated by chromatography on silica. Dehydration of the mixture **9** on heating with *p*-TsOH in toluene provided the desired thioamides **5** (method A). On the other hand, treatment of the mixture **9** with *p*-toluenesulfonyl chloride (*p*-TsCl) in pyridine gave the corresponding amides **10**, which were converted to the thioamides **5** by heating with Lawesson's reagent in benzene (method B).

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**),[4] pinacidil (**2**),[5] and RP49356 (**3**).[6]

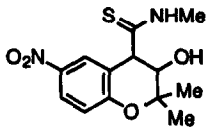
The intermediates β-keto thioamides **8a** and β-hydroxy thioamides **9aa** and **9ab** showed only about 100 to 1000 times less potent vasorelaxant activity than the benzopyran **5a**. Arch *et al.*[7] have also reported similar results on the relaxant activity in guinea pig trachealis of the 6-cyano analogs.

The 2,2-dimethyl compound **5a** possessed very potent vasorelaxant activity and was about 10-fold more potent than the corresponding 6-cyano analog **4** (X=S)[2a] and about 100-fold more potent than the reference compounds **1**-**3**. Increase in the size of 2,2-dimethyl group of **5a** (compare **5a** with **5b**-**5e**) enhanced the activity except **5d**, 2-methyl-2-*n*-propyl derivative **5c** being optimum. On the contrary, 2-ethyl compound **5f** was devoid of the activity. However, increase in the size of the 2-ethyl group to 2-*t*-butyl group (**5g**) restored the activity to the high level. Cyclization of the 2-substituent to 2-spiro compounds **5h** and **5i** enhanced or retained the vasorelaxant activity. Enlargement in size of the 2-spiro ring to give compounds **5j**-**l** was detrimental to potency. The $pEC_{50}$ values of the most potent compounds **5c**, **5h**, and **5i** are 10.60 to 10.77. These are about 10,000 times more potent than cromakalim (**1**). To our knowledge, these compounds **5c**, **5h**, and **5i** seem to be the most potent $K^+$ channel openers known to date.[8]

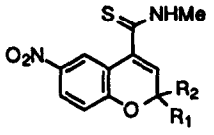
**Table I.** Physical properties and vasorelaxant activity of benzopyran-4-carbothioamides (**8a**, **9aa**, **9ab**, and **5a-l**)




**8a**




**9aa, 9ab**

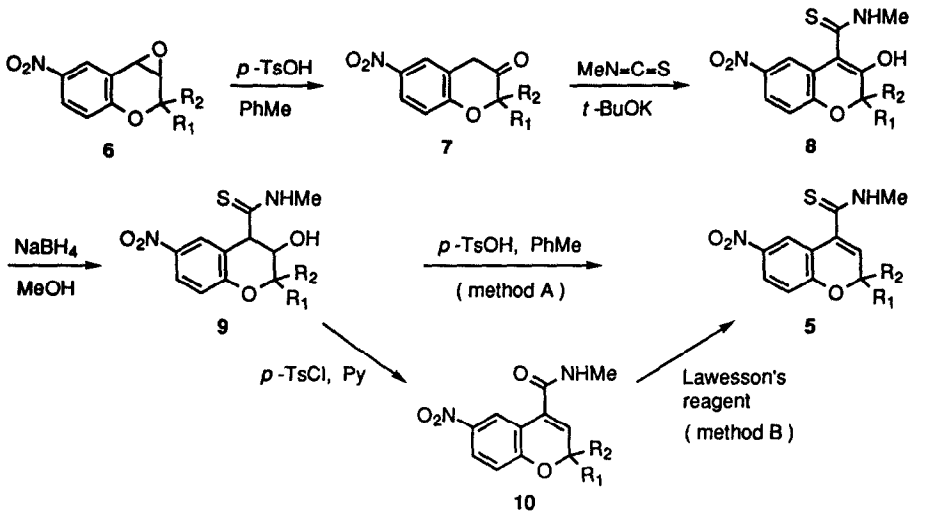



**5a-l**

| Compd. | $R_1$ | $R_2$ | method | % yield[a] | mp, ℃ | rat aorta $pEC_{50}$[b] | rat aorta IA (%)[c] | rat aorta n[d] |
|---|---|---|---|---|---|---|---|---|
| **8a** | | | | | 148-149 | 5.95±0.16 | 93.9±3.1 | 3 |
| **9aa**[e] | | | | | 181-183 | 6.96±0.14 | 57.9±3.3 | 3 |
| **9ab**[f] | | | | | 205-207 | 6.58±0.03 | 73.2±2.2 | 3 |
| **5a**[g] | Me | Me | B | 87 | 147-148 | 8.87±0.05 | 63.5±4.7 | 5 |
| **5b** | Me | Et | A | 38 | 139-140 | 9.74±0.15 | 75.1±2.7 | 3 |
| **5c** | Me | *n*-Pr | A | 32 | oil | 10.77±0.34 | 62.6±7.9 | 5 |
| **5d** | Me | *n*-Bu | B | 86 | oil | 7.39±0.11 | 66.5±0.8 | 3 |
| **5e** | Et | Et | B | 2 | 127-128 | 9.43±0.25 | 70.3±3.7 | 3 |
| **5f** | H | Et | B | 77 | 94-96 | <4.5 | | 3 |
| **5g** | H | *t*-Bu | B | 70 | 156-157 | 9.40±0.30 | 71.7±1.0 | 3 |
| **5h** | $-(CH_2)_3-$ | | B | 18 | 165-166 | 10.68±0.12 | 68.2±5.1 | 3 |
| **5i** | $-(CH_2)_4-$ | | B | 8 | 191-192 | 10.60±0.21 | 77.7±6.6 | 3 |
| **5j** | $-(CH_2)_5-$ | | A | 49 | 213-215 | 9.95±0.21 | 77.6±3.8 | 3 |
| **5k** | $-(CH_2)_6-$ | | A | 30 | 158-159 | 7.32±0.14 | 61.5±5.1 | 3 |
| **5l** | adamantyl | | B | 22 | 253-257 | 6.39±0.22 | 87.9±5.3 | 3 |
| 4 (X=S)[h] | | | | | | 7.61±0.07 | 89.0±2.5 | 4 |
| 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]Cis 3,4 isomer. [f]Trans 3,4 isomer. [g]See reference 2b. [h]See reference 2a.

**Scheme I**

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