Bioorganic & Medicinal Chemistry Letters, Vol.3, No.8, pp. 1659-1662, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

STRUCTURE-ACTIVITY RELATIONSHIPS OF 6-SUBSTITUTED BENZOPYRAN-4-CARBOTHIOAMIDE POTASSIUM CHANNEL OPENERS

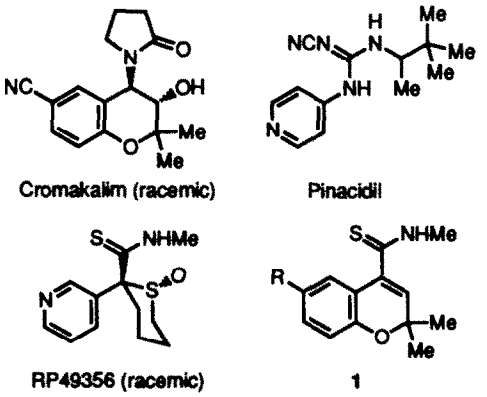
Takenori Ishizawa, Hiroshi Koga,* Masateru Ohta, Haruhiko Sato, Toshihiko Makino, Kiyonori Kuromaru, Naoki Taka, Tadakatsu Takahashi, Tsutomu Sato, and Hiroyuki Nabata

Fuji-Gotemba Research Laboratories, Chugai Pharmaceutical Company, Ltd., 135, 1-Chome Komakado, Gotemba-shi, Shizuoka, 412, Japan

(*Received in USA* 5 *April* 1993)

Abstract. QSAR study of 6-substituted benzopyran-4-carbothioamides **1** showed that vasorelaxant activity is linearly correlated with the electronic parameter (σ_m) and parabolically correlated with steric (L) and hydrophobic (π) parameters of the 6-substituent.

Currently, considerable attention has been focused on potassium channel openers, because they are believed to be potential drugs for diseases such as hypertension, angina pectoris, asthma, and alopecia.[1] It is recognized that these potassium channel openers constitute a chemically diverse type of compounds. Cromakalim, pinacidil, and RP49356 are the representatives. Although none of these compounds is structurally related to any of the others, they are thought to exert the smooth muscle relaxant activity through the opening of ATP-sensitive potassium channels and the binding sites for these openers are assumed to be at least in part the same from their pharmacological and receptor binding studies.[1,2]



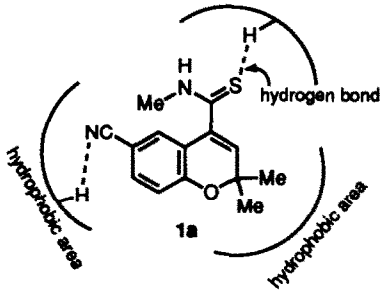


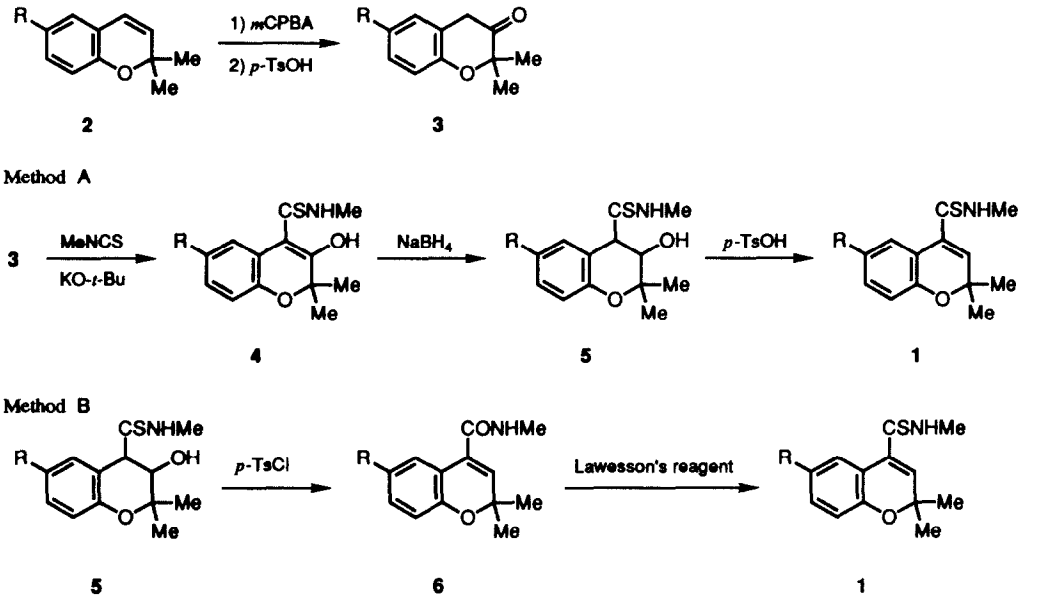
Figure 1. Schematic representation of proposed pharmacophore model of potassium channel openers

We previously defined a pharmacophore model of potassium channel openers and designed new potassium channel openers using this model (Figure 1).[3] One of these was benzopyran-4-carbothioamide **1a** which exhibited higher activity than cromakalim, pinacidil, and RP49356. Although it is expected that the 6-cyano group of **1a** works as a hydrogen-bond acceptor from the pharmacophore model (Figure 1), further study is needed to rationally explain the function. Qualitative structure-activity relationship studies on cromakalim derivatives revealed that activity varied with the σ_p value of the electron withdrawing group at the 6-position.[1,4,5]

However, little has been reported about the quantitative study. In this paper, we wish to report the quantitative structure-activity relationships (QSAR) of 6-substituted benzopyran potassium channel openers **1**.

Compounds of general formula **1** were prepared by the procedure similar to that reported for **1a** (Scheme I and Table I).[3,6] Thus, compound **2** was converted by epoxidation (*m*CPBA, CH_2Cl_2, *room temp.*, 1 day) and subsequent rearrangement (*p*-TsOH, toluene, reflux, 2 h.) to ketone **3**. The thioamide **4** obtained by acylation of **3** with methyl isothiocyanate (KO-*t*-Bu, DMF, 0 °C, 12 h.) was reduced to give alcohol **5** ($NaBH_4$, MeOH, THF, 0 °C, 12 h.), as a mixture of cis and trans isomers. Compound **5** was dehydrated to the desired **1** (*p*-TsOH, toluene, reflux, 2 h.) (method A). Alternatively, compound **5** was converted to 4-carboxamide derivative **6** (*p*-TsCl, pyridine, reflux, 2 h.). Compound **1** was obtained by thiation of **6** (Lawesson's reagent, benzene, reflux, 1 h.) (method B).

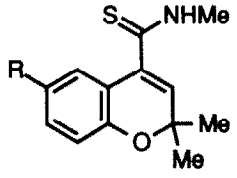
Scheme I



The vasorelaxant activities of **1** were determined by the effects on 30 mM KCl response in rat aorta and are listed in Table I in comparison with cromakalim.[5] The potassium channel opening property was comfirmed by the ability of glibenclamide, an ATP-sensitive potassium channel blocker, to inhibit the vasorelaxation caused by selected compounds.[1,6,7] Among tested compounds, 6-nitro compound **1b** was the most potent and about 100-fold more potent than cromakalim.

QSAR analysis[8] for compounds of type **1** showed that, in addition to the expected electronic parameter (σ_m) vasorelaxant activity is significantly correlated with hydrophobic (π) and steric (L) parameters of the 6-substituents, as shown in equation 1. In this equation, σ_m is Hammett constant[9] of R substituent of compound **1**, π stands for the hydrophobic constant[9] of R, L is Verloop's STERIMOL parameter[9] representing the length of R, the figures in parentheses are the 95% confidence intervals, n is the number of data points employed, r is the correlation coefficient, and s is the standard deviation from regression. The term L is significant at >94%

Table I. Vasorelaxant Activities of 6-Substituted Benzopyran-4-carbothioamides **1** and Parameters for the Formulation of QSAR Equation



1

No.	R	method	Yield (%)	mp (°C)	pEC_{50} [a]	IA (%) [b]	n [c]	Calcd. [d]	Δ [e]	σ_m [f]	L [f]	π [f]
1a	CN [g]	A	44	139-141	7.61± 0.07	89.0± 2.5	4	7.74	-0.13	0.56	4.23	-0.57
1b	NO_2	A	52	147-148	8.87± 0.05	63.5± 4.7	5	8.70	0.17	0.71	3.44	-0.28
1c	$PhSO_2$	A	44	93-95	7.72± 0.16	73.7± 0.8	3	7.71	0.01	0.61	5.86	0.27
1d	$MeSO_2$	A	23	138-141	6.34± 0.00	69.8± 3.0	3	6.22	0.12	0.60	4.37	-1.63
1e	CF_3	B	76	150-151	8.69± 0.28	73.0± 4.3	5	8.21	0.48	0.43	3.30	0.88
1f	C_2F_5	B	92	153-154	7.90± 0.15	55.4± 8.8	3	8.22	-0.32	0.47	4.11	1.89
1g	CF_3O	A	66	159-160	8.39± 0.12	76.1±10.1	3	7.92	0.47	0.38	4.57	1.04
1h	MeOCO	A	15	206-207	7.02± 0.12	76.1± 3.8	3	7.30	-0.28	0.37	4.85	-0.01
1i	Br	B	66	136-138	8.03± 0.21	67.5± 2.7	3	8.09	-0.06	0.39	3.83	0.86
1j	Cl	B	30	138-140	7.43± 0.09	73.1± 3.0	3	7.96	-0.53	0.37	3.52	0.71
1k	H	A	57	122-123	5.37± 0.12	89.3± 4.2	3	5.42	-0.05	0.00	2.06	0.00
1l	Et	A	21	110-111	6.49± 0.11	78.7± 6.5	3	6.21	0.28	-0.07	4.11	1.02
1m	MeO	A	27	107-108	6.38± 0.02	61.5± 6.1	3	6.54	-0.16	0.12	3.98	-0.02
Cromakalim					6.77± 0.03	74.7± 2.1	25					

[a] Negative logarithms of the molar concentration required to relax rat aorta precontracted with 30 mM KCl by 50% of IA, with ± SEM. See footnote 10 for experimental details. [b] Intrinsic activity ± SEM (%). [c] Number of determinations. [d] Calculated by eq. 1 (pEC_{50}). [e] Difference between observed and calculated values. [f] Parameters for the 6-substituent. See reference 9. [g] References 3 and 6.

level. This equation suggests that compounds **1** with an electron withdrawing group at the 6-position possess high vasorelaxant activity. This equation also shows that the activities of 6-substituted compound **1** are parabolically correlated to the hydrophobic (π) and steric (L) parameters of the 6-substituent. These results, together with those obtained from the pharmacophore model previously constructed,[3] comfirm that electronic, hydrophobic, and steric effects of the 6-substituent contribute at least in part to the binding of compound **1** to the receptor.

$$\begin{aligned} pEC_{50} = {} & 4.067\ (\pm 1.352)\ \sigma_m + 0.791\ (\pm 0.331)\ \pi - 0.347\ (\pm 0.275)\ \pi^2 \\ & + 1.756\ (\pm 1.825)\ L - 0.234\ (\pm 0.224)\ L^2 + 2.794 \qquad (1) \\ & n = 13,\ r = 0.957,\ s = 0.393,\ \text{ideal}\ \pi = 1.14,\ \text{ideal}\ L = 3.75 \end{aligned}$$

References and Footnotes

1. a) Robertson, D. W.; Steinberg, M. I. *J. Med. Chem.* **1990**, *33*, 1529. b) Edwards, G.; Weston, A. H. *Trends Pharmacol. Sci.* **1990**, *11*, 417. c) Evans, J. M.; Longman, S. D. *Ann. Rep. Med. Chem.* **1991**, *26*, 73.
2. Bray, K. M.; Quast, U. *J. Biol. Chem.* **1992**, *267*, 11689.
3. Koga, H.; Ohta, M.; Sato, H.; Ishizawa, T.; Nabata, H. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 625.
4. Attwood, M. R.; Jones, P. S.; Kay, P. B.; Paciorek, P. M.; Redshaw, S. *Life Sciences* **1991**, *48*, 803.
5. Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194.
6. Arch, J. R. S.; Buckle, D. R.; Carey, C.; Parr-Dobrzanski, H.; Faller, A.; Foster, K. A.; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith, D. G.; Taylor, S. G. *J. Med. Chem.* **1991**, *34*, 2588.
7. Imagawa, J.; Nabata, H., unpublished results.
8. For QSAR regressions, parameters were chosen to reflect the electronic, hydrophobic, and steric effects due to change in R. A total of ten parameters (σ_m, σ_p, π, π^2, L, L^2, B_1, B_1^2, B_4, and B_4^2) was examined as descriptors. Since this is somewhat large for a 13-membered compound set (Topliss, J. G.; Edwards, R. P. *J. Med. Chem.* **1979**, *22*, 1238), limitations were applied to reduce the risk of finding spurious relationships. The electronic parameters σ_m and σ_p were not considered simultaneously and the steric parameters L, B_1, and B_4 were also not. Combinations with squared terms were not allowed unless both the variable and its square met the significance criterion. No combinations containing more than five terms were considered. The validity of QSAR equation 1 obtained, was also evaluated by cross-validation (Wold, S. *Quant. Struct.-Act. Relat.* **1991**, *10*, 191: Cramer, R. D. III; Bunce, J. D.; Patterson, D. E. *Quant. Struct.-Act. Relat.* **1988**, *7*, 18). The result (leave-one-out technique) was a cross-validated r^2 of 0.586, so this equation seems to be a reasonable QSAR model.
9. *Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: Oxford, 1990; Vol 4.
10. 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 (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 at the level of a force-displacement transducer (Nihon Kohden, 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 reduction of 30 mM KCl contraction. The intrinsic activity (IA) for each compound was calculated as a percentage of its maximum reduction of 30 mM KCl contraction. Only one concentration-relaxation curve was obtained from each preparation.