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ANTIHYPERTENSIVE BENZOPYRAN-RELATED POTASSIUM CHANNEL ACTIVATORS: A ROLE FOR LIPOPHILICITY

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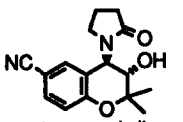
Abstract: A series of benzopyran-related potassium channel activators were prepared and evaluated at the calculated ED_{30} dose in the spontaneously hypertensive rat. The duration of the blood pressure lowering effect was found to be related to the lipophilicity of the agent and was independent of the potency.

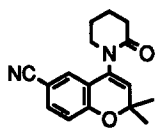
Potassium channel openers (KCOs) are an emerging group of structurally diverse, synthetic compounds whose pharmacological basis involves the opening of a glibenclamide sensitive potassium channel, thereby effecting hyperpolarization of the cellular membrane.[1] These agents offer novel therapeutic approaches to diseases of the cardiovascular system (e.g. hypertension, angina pectoris), asthma, and irritable bladder syndrome, and present future therapeutic prospects for treating ischemia (chronic occlusive arterial disease, cerebral vasospasm), epilepsy, and impotence.[2]

With respect to the medicinal chemistry of the KCOs, the benzopyran scaffold has been exploited most,[3] yielding agents such as cromakalim (**1a**) and its eutomer lemakalim (**1b**),[4] EMD-52,692 (**2**),[5] Ro-31-6930 (**3**),[6] SDZ-PCO-400 (**4**),[7] and NIP-121 (**5**).[8] In the course of our investigations of the benzopyran KCOs, we were intrigued by the antihypertensive profile of **6**, the eutomeric form of which (3S,4R; WAY-120,491; celikalim) was chosen for further development.[9] Whereas cromakalim (**1a**) was more potent than **6** in the spontaneously hypertensive rat (SHR), **6** exhibited prolonged duration of action compared to cromakalim at equihypotensive doses (Table 1). These results are particularly noteworthy since changes in the C-4 and C-6 benzopyran substituents completely dissociate antihypertensive potency from duration of action.

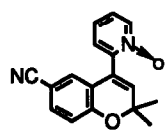
To further probe physicochemical parameters which may contribute to the in vivo profile of antihypertensive KCOs, additional derivatives **7 - 10** were prepared and evaluated in the SHR. We wish to report that the overall lipophilicity of the compound appears to be a major contributor to the antihypertensive effects of these agents.



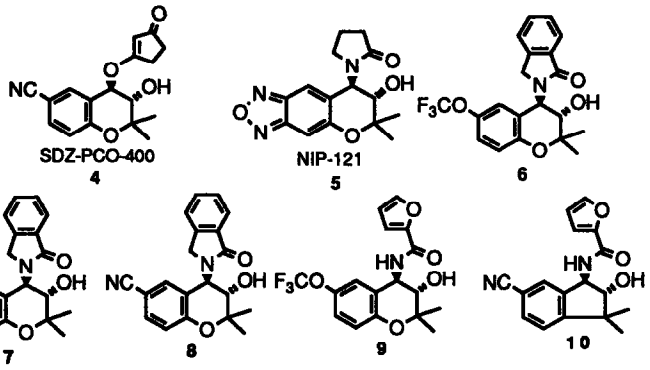
1 a cromakalim
1 b lemakalim (3S,4R)



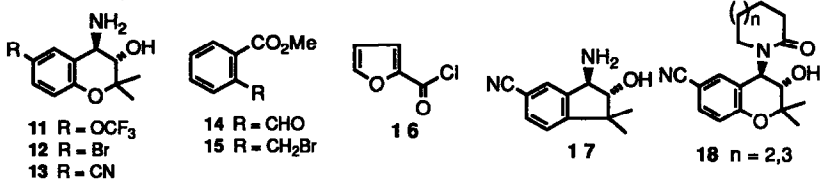
EMD-52,692
2



Ro-31-6930
3



The synthesis of **6** from amino alcohol **11** was described previously.[10] Isoindolone **7**, mp 207 - 208 °C, was prepared from **12**[11] in 85% yield by reductive amination with **14** using the reductive amination procedure described previously,[10] followed by catalytic hydrogenation (H_2, 10% Pd / C, MeOH). Isoindolone **8**, mp 238 - 239 °C, was prepared in 39% yield by alkylation/cyclization of amino alcohol **13**[12] with **15**.[10,13] Derivatives **9**, mp 146 - 147 °C, and **10**, mp 176 - 177 °C, were fashioned in 50% yield from **11** and **17**,[14] respectively, by treatment with **16** in the presence of triethylamine.



Compounds **6** - **10** were evaluated first for potency. The dose that lowered blood pressure by 30%[15] was calculated by regression analysis of the dose response curve The agents were then studied at the calculated ED_{30} for duration of action in the SHR (Table I)[16] and were compared to cromakalim. It is clear from the data that variation about C-4 or C-6 of the benzopyran nucleus or modification of the benzopyran nucleus, as in **10**,[17] dramatically affects both the potency and duration. Electron withdrawing substituents about C-6 of the benzopyran ring enhanced antihypertensive effect (i.e. **8** > **6** > **7**),[18] consistent with previous reports.[19]

On the other hand, replacement of the C-4 pyrrolidinone moiety of cromakalim with the bulky isoindolone grouping as in **8** enhanced potency, showing the exquisite sensitivity of antihypertensive potency towards the nature of the C-4 substituent.[17] By comparison, increasing the number of intervening carbons of the cromakalim lactam as in **18** is reported to dramatically decrease antihypertensive potency.[19]

Our results further indicate that within benzopyran-related KCOs, the duration of blood pressure lowering effects at equihypotensive doses correlates with overall lipophilicity, irrespective of the

substitution about the C-4 amide, C-6 substituent, or benzopyran framework (i.e. **10**), and that this effect is independent of potency. Thus, the lipophilic hypotensive agents **6** and **9** possess the longest duration of action at the calculated ED_{30} dose. The hypotensive effects of trifluoromethoxy derivative **6** last considerably longer than more hydrophilic agents such as cromakalim, **8**, or indan **10**. Conversely, the most hydrophilic compounds, cromakalim (**1a**) and **10**, possess the shortest duration of action.

In conclusion, lipophilicity appears to play a major role in the in vivo profile of benzopyran-related antihypertensive KCOs. The results of this study should be of value in the rational design of this class of antihypertensive agents.

Table I: Antihypertensive Profile of Potassium Channel Activators[§] in the Spontaneously Hypertensive Rat[20]

Compound	Dose (mg/kg, p.o.)	n	Mean Arterial Pressure		Duration (hr)	clogP[21]
			Pretreatment (mmHg)	% max change		
1a	0.17	8	171 ± 2	-28 ± 2	2 - 3	1.1
6	0.50	8	180 ± 1	-28 ± 1	24	3.5
7	2.5	4	184 ± 9	-26 ± 1	>5~	2.3
8	0.03	8	173 ± 4	-23 ± 2	8	2.1
9	2.1	6	175 ± 3	-30 ± 2	24	3.2
10	1.5	4	182 ± 3	-35 ± 3	3	1.5
control*	0	6	172 ± 4	-3 ± 5		

§ Compounds were tested as racemic mixtures.
*Control group was administered 0.5% methylcellulose.
~Experiment terminated after 5 hr. Blood pressure was decreased by 11± 1% at this point. By comparison, the blood pressure was still depressed by 28% after 5 hr with **6**.

REFERENCES

1. (a) Robertson, D. W.; Steinberg, M. I. *J. Med. Chem.* **1990**, 33, 1529. (b) Edwards, G.; Weston, A. H. *Trends Pharmcol. Sci.* **1990**, 417. (c) Cook, N. S.; Quast, U. In "Potassium Channels: Structure, Classification, Function and Therapeutic Potential;" Cook, N. S., Ed.; Ellis Horwood Limited: Chichester, West Sussex , England, 1990; p 181.

2. Duty, S.; Weston, A. H. *Drugs*, **1990**, 40, 785.

3. McCaully, R. In "Current Drugs: Potassium Channel Modulators;" Weston, A. H., Ed.: Current Drugs; London, England, in press.

4. Hof, R. P.; Quast, U.; Cook, N. S.; Blarer, S. *Circ. Res.* **1988**, 62, 679. Buckingham, R. E.; Clapham, J. C.; Hamilton, T. C.; Longman, S. D.; Norton, J.; Poyser, R. H. *J. Cardiovasc. Pharmacol.* **1986**, 8, 798. Clapham, J. C.; Hamilton, T. C.; Longman, S. D.; Buckingham, R. E.; Campbell, C. A.; Isley, G. L.; Gout, B. *Arzneim.-Forsch/Drug Res.* **1991**, 41, 385.

5. Bergmann, R.; Eiermann, V.; Gericke, R. *J. Med. Chem.***1990**, 33, 2759.

6. Attwood, M. R.; Jones, P. S.; Kay, P. B.; Paciorek, P. M.; Redshaw, S. *Life Sci.* **1991**, 48, 803.

7. Fozard, J. R.; Menninger, K.; Cook, N. S.; Blarer, S.; Quast, U. *Br. J. Pharmacol. Proc. Suppl.* **1990**, 99, 7P.

8. Masuda, Y. Arakawa, C.; Yamashita, T.; Miyajima, M. Shigenobu, K.; Kasuya, Y.; Tanaka, S. *Eur. J. Pharmacol.* **1991**, 195, 323.

9. (a) Morin, M. E.; Wojdan, A.; Oshiro, G.; Colatsky, T.; Quagliato, D. *Fed. Am. Soc. Exp. Biol. J.* **1990**, 4, 2785. (b) Lodge, N. J.; Cohen, R. B ; Havens, C. N.; Coltasky, T. J. *J. Pharmacol. Exp. Ther.* **1991**, 256, 639.

10. Quagliato, D. A.; Humber, L. G.; Joslyn, B. L. Soll, R. M.; Browne, E. N. C.; Shaw, C. C.; Van Engen, D. *Biomed. Chem. Lett.* **1991**, 39. Procedure for **7** from **12**: To 1.73 g (6.36 mmol) of **12** in 10 mL of methanol was added 1.36 g (8.37 mmol) of **14** followed by 25 mL (12.5 mmol) of methanolic $NaBH_3CN$ /$ZnCl_2$ solution (described by Kim, S. H.; Oh, C. H ; Ko, J. S.; Ahn, K. H.; Kim Y. J. *J. Org. Chem.***1985**, 50, 1927) After stirring at 45 °C for 72 hr, the reaction mixture was quenched with water, extracted into methylene chloride, dried (K_2CO_3), and concentrated. The residue was suspended in a small amount of methylene chloride and the solid was collected (1.16 g, 47%) Additional product was obtained by recrystallization of the mother liquor. A solution of 1.01 g (2.61 mmol) of product in methanol was hydorgenated (50 psi initial H_2 pressure) over 10% Pd/C. Filtration through solka floc and purification by flash chromatography (20% ether/ methyene chloride) gave 690 mg (85% yield) of **7**.
Procedure for **8** from **13**· A mixture of 45.0 g (90.206 mol) of **13**, 49.6 g (0.216 mol) of **15**, 62.6 g (0 45 mol) of potassium carbonate, and 17.1 g (0.10 mol) of potassium iodide in 500 mL of acetonitrile was heated at 70 °C for 16 hr. The reaction mixture was quenched with water, and extracted into ethyl acetate. The organic extract was washed with sodium thiosulfate, dried (Na_2SO_4). and flash chromatographed (20% ethyl acetate/methylene chloride) to provide **8** and uncyclized material The uncyclized compound was heated in refluxing toluene for 5 hours. Cooling to room temperature and trituration with cold ether provided pure **8**. Total yield: 26.9 g (39%).

11. Shiokawa, Y ; Takimoto, K; Takenaka, K; Kato, T. *EP 389861 A1*, 3 Oct 1990.

12. Evans, J. M.; Buckingham, R E.; Wilcocks, K. *EP076075 A1*. 21 Sept 1982.

13. Hellwinkel, D.; Siegbert, B *Chem. Ber.* **1987**, 120, 1151.

14. Stemp, G ; Burrell, G ; Smith, D. G. *EP359537 A1*, 21 Mar 1990.

15. The difference in mean arterial blood pressure between spontaneously hypertensive and normotensive rats is approximately 30%. For an anithypertensive compound to be therapeutically effective it should decrease blood pressure by 30% to bring blood pressure into the normotensive range. It is then possible to make comparisons of oral potency and duration of action between drugs· Oshiro, G.; Wojdan, A.; Klein, M.; Metcalf, G. *J. Cardiovasc. Pharmacol.* **1987**, 10, 341.

16. The duration of action is determined by the last time point which is statistically different from the pretreatment control blood pressure.

17 For the synthesis and evaluation of a series of related indanols as smooth muscle relaxants, see: Buckle, D. R ; Arch, J. R. S.; Edge, C., Foster, K. A ; Houge-Frydrych, C. S. V.; Pinto, I. L.; Smith D. G.; Taylor, J. F.; Taylor, S G.; Tedder, J M ; Webster, A. B. *J Med. Chem.***1991**, 34, 919.

18. σ_p for CN, OCF_3, and H are 0.66, 0.35, and 0.00, respectively. "Substituent Constants for Correlation Analysis in Chemistry and Biology;" Hansch, C , Leo, A.; John Wiley and Sons: New York, 1979; Table IV-1, p 49

19. 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.

20. Spontaneously hypertensive rats ranging in weight from 305 - 370 g obtained from Charles River (Lakeview, MA) were used for this study. The rats were anesthetized with halothane, and the left femoral vein and artery cannulated with polyethylene tubing (PE50). The rats were placed in Bollman cages and the arterial cannula connected to a Gould-Statham pressure transducer (Model P23Db), which in turn was attached to a polygraph to record mean arterial blood pressure (MABP). The animals were allowed at least one hr to recover from anesthesia. The compounds were suspended in 0.5% solution of methylcellulose and were administered by gastric gavage in a volume of 5 mL/kg. A similar volume of methylcellulose solution only was given to a group of rats that served as vehicle-treated controls. MABP was recorded prior to and then continuously for 24 hr after compound administration.

21. MedChem Program V3 54.