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DIHYDROPYRIDINE K_{ATP} POTASSIUM CHANNEL OPENERS

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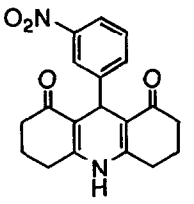
Abstract: Three related series of dihydropyridine K_{ATP} potassium channel openers are described.

Dihydropyridines (DHPs) are a well known class of Ca^{++} blockers that are established in the clinic as vasodilators and antihypertensives. We wish to report that we have discovered that a particular series of DHPs, represented by **1**, are novel K_{ATP} potassium channel openers (PCOs). **1** was initially screened for PCO activity as it contains an aromatic ring bearing an electron withdrawing group (i.e. NO_2) which is positioned orthogonally to a second ring containing an adjacent hydrogen bond acceptor group. This perpendicular arrangement of an electron deficient aromatic moiety and hydrogen bond acceptor group is present in both low energy conformations[1] and in the x-ray conformation[2] of cromakalim **2** and we hypothesized that this relationship might be the pharmacophore responsible for PCO activity in cromakalim-like compounds. Compound **1** and derivatives have been claimed to be smooth muscle relaxants[3] and two hetero derivatives were claimed to be Ca^{++} blockers[4] but there has been no prior report on the potassium channel opening activity of this series. The DHP (+)-niguldipine however has been shown by the voltage clamp technique to activate the Ca-dependent maxi K-channel (BK_{Ca}) in inside-out patches from vascular smooth muscle cells[5].



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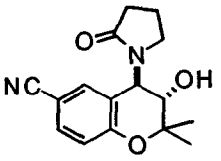

(±) **2**

Our program was aimed at the discovery of a PCO appropriate for use in urinary urge incontinence. Thus compounds were screened as relaxants of 15mM precontracted guinea pig detrusor or spontaneously active guinea pig portal vein.[7] Data for **1** and the most active PCO of this series, **3**, is shown in table I. By comparison, (+)-niguldipine is inactive in the bladder strip model.

In a set of experiments designed to establish that **1** was a PCO at the K_{ATP} channel, **1** was tested against guinea pig detrusor strip contracted with 80 mM KCl. An IC_{50} of 47.8 ± 6.6μM suggested a profile of action that is consistent with a PCO. The relaxant effects of **1** (15mM KCl) are reversed by glibenclamide (pK_b = 7.3), a relatively selective blocker of K_{ATP}. Compound **1** (50μM) was also shown to increase the maximum $^{86}Rb^+$ (a K^+ surrogate) efflux rate constant from guinea pig detrusor by 30.7 ± 5.9% (30μM cromakalim caused a 47.2 ±11.6% increase).

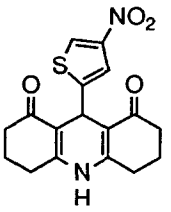

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Table I

Compound	IC50 (μM)	
	G.P. Detrusor[6]	G.P. Portal Vein[6]
1	4.44 ± 0.50	0.10 ± 0.02
2	0.57 ± 0.07	0.020 ± 0.004
3	0.16 ± 0.01	0.009 ± 0.001
(-)niguldipine	>30	
(+)niguldipine	>30	

A SAR analysis carried out on phenyl ring substitution indicates that electron withdrawing groups are optimal for PCO activity with position 3 > 4 >> 2 and with 3,5 disubstitution inactive. The most active phenyl substituents discovered are 3,4-disubstituted (3-Cl, 4-F = 0.46 μM; 3-CF_3, 4-CN = 0.42 μM). Lower alkyl in the 3 or 4 position yields modestly active derivatives (5 - 25 μM) although the 4-phenyl derivative is surprisingly active at 1.37 μM. N-methyl substitution of **1** gave an inactive compound. Thus in addition to a perpendicular arrangement of an electron deficient aromatic moiety and hydrogen bond acceptor group there may also be a SAR requirement for a free NH in this class of potassium channel openers. In the DHP Ca^{++} blockers the DHP NH is hypothesized to hydrogen bond to the receptor[8].

The monoketo derivatives shown below are even more potent PCOs in the phenyl series as illustrated in Table II.

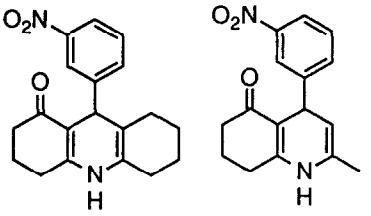

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Table II

Compound	IC50 (μM)
	G.P. Detrusor[6]
1	4.44 ± 0.50
4	0.51 ± 0.02
5	0.66 ± 0.05

It is of interest to determine if the PCO activity of the above series resides primarily in one of the enantiomers. That work is in progress.

References and Notes

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