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ANILIDE TERTIARY CARBINOLS: A NEW STRUCTURAL CLASS OF POTENT POTASSIUM CHANNEL OPENERS

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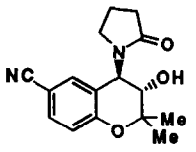
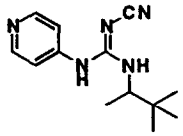
Abstract: A new structural class of anilide tertiary carbinol potassium channel openers (PCOs) is described.

Potassium channels are known to play a key role in controlling cellular excitability. As the predominant charge carrying ion channel in resting cells, potassium channels are major contributors to the resting cell potential. They are also involved in action potential duration, after-hyperpolarization, and thus in events related to the rate of firing of an action potential. Modulation of these factors is important in the control cellular excitability.[1]



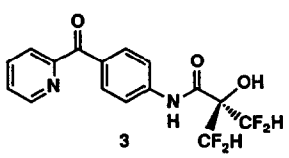
(±) 1



(±) 2

A number of structurally diverse agents have been described that function by opening potassium channels, primarily ATP-sensitive potassium channels, in a number of different tissues and cell types.[1] The discovery of the PCO cromakalim (**1**),[2,3] and the subsequent realization that pinacidil, (**2**) also functioned as a hypotensive agent by virtue of its PCO properties led to an explosion of interest in potassium channels.[4] Other structurally distinct PCOs have also been described. Therapeutic applications of PCOs in hypotension and in asthma are being explored by a number of companies. Our interest has been primarily in the area of urinary urge incontinence (UI).

An investigation of a sub-set of anti-androgen compounds possessing unwanted hypotensive activity resulted in the discovery of a new structural class of potassium channel openers.[5] This series is represented by the tertiary carbinol **3** which has been found to be *ca.* eight fold more potent than the racemic cromakalim, (**1**) on guinea-pig detrusor (bladder) strip mildly depolarized with 15mM KCl.[6] On vascular tissue (guinea-pig portal vein) **3** was found to be *ca.* seven times more potent than **1** as shown in Table 1.

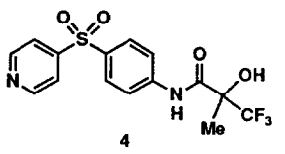


3

Compound	IC_{50} (μM)[7]	
	G.P. Detrusor	G.P. Portal vein
1	0.57±.07	0.020±0.004
3	0.070±0.007	0.0030±0.0005

Table 1.

Although **3** is achiral we have also investigated compounds such as **4** and have found that the PCO activity largely resides in the S enantiomer **5** as shown in Table 2.



4

Compound	IC_{50} (μM)
	Detrusor strip
4 (±)	3.80±0.51
5 (4 (S)(-))	1.6±0.2
6 (4 (R)(+))	>30

Table 2.

The PCO activity of this series has been confirmed in a number of supporting studies. Thus the relaxant effects of **5** on guinea-pig detrusor are reversed by the specific K_{ATP} blocker, glibenclamide ($pA_2 = 7.2$). Additionally the relaxant activity of **5** under highly depolarized conditions (using 80mM KCl) is very weak ($IC_{50} = ca.$ 260μM). We have also demonstrated that **5** will increase the rate of efflux of $^{86}Rb^+$ (A K^+ surrogate) from guinea-pig detrusor smooth muscle. A 40.0 ± 4.5% maximum increase in the efflux rate constant was obtained with 54.6μM of **5** using guinea pig detrusor (30μM cromakalim caused a 47.2 ±11.6% increase).

It is of interest to note that **3** has a pKa of *ca.* 7.5 making it *ca.* 50% ionized at a physiological pH of 7.4. Glibenclamide has a similar pKa and this has been exploited to help understand whether this agent binds to an extracellular, intracellular, or intramembrane site.[8] Conceivably similar experiments could be performed with **3** or related ionized PCOs to help locate the interaction site of these PCOs. To our knowledge **3** is the first reported example of a PCO to be ionized to a significant degree at physiological pH.

In summary we report a new structural class of potent potassium channel openers that interact with the K_{ATP} channel in guinea-pig detrusor smooth muscle.

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5 Gibson, K.; Grant, T; Todd, M., Manuscript in preparation.
6. Details of the preparation of the anilide tertiary carbinols in this paper are available in patent EP 524 781 and will also be described in a forthcoming full paper
7. Relaxation was measured either using a 15mM KCl contracted strip (Guinea-pig detrusor) or using spontanoeus activity (Guinea-pig portal vein). For details see Zografos, P.; Li, J. H.; Kau, S. K. Comparison Of The In Vitro Effects Of K^+ Channel Modulators On Detrusor And Portal Vein Strips From Guinea Pigs. *Pharmacology*, **1992**, *45*, 216.
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