Bioorganic & Medicinal Chemistry Letters, Vol.3, No.12, pp. 2727-2728, 1993
Printed in Great Britain

0960-894X/93 $6.00 + .00

A HIGHLY POTENT SERIES OF FLUOROALKYL BENZOXAZINE PYRIDINE-N-OXIDE POTASSIUM CHANNEL OPENERS

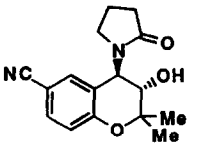
K. Russell[§*], F. J. Brown[§*], P. Warwick[§], J. Forst[§], T. Grant[†], B. Howe[†], S. T. Kau[†], J. H. Li[†], F. M. McLaren[§], H.S. Shapiro[§], S. Trivedi[†]

[§]*Medicinal Chemistry Department and* [†]*Pharmacology Department, ZENECA Pharmaceuticals Group. A Business unit of ZENECA Inc., Wilmington, DE 19897*

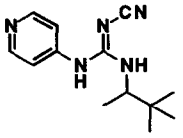
(*Received in USA* 21 *June* 1993; *accepted* 27 *September* 1993)

Abstract: A new structural class of fluoroalkyl benzoxazine pyridine-N-oxide potassium channel openers (PCOs) is described.

Cellular excitability is ultimately determined in many instances by the transmembrane potential of the cell.[1] Since potassium channels are the main charge carrying ion channels in most cells they largely control the resting membrane potential and thus the basal excitability level. Potassium channel also govern cellular excitability by influencing the rate and duration of firing of action potentials. Agents that effect the gating of these channels would thus be expected to modify cellular excitability.[1]



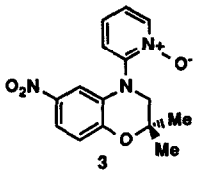
(±) 1



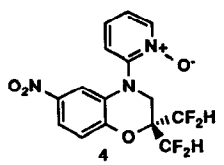
(±) 2

A number of 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**),[1,2] 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.[3] 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).

As part of a program aimed at finding potassium channel openers for use in UI we have investigated a series of benzoxazine pyridine-N-oxides as exemplified by **3**. Matsumoto and coworkers have recently disclosed their work with this structural class of PCOs.[4] Indeed it is reported that **3** (YM-934) is being progressed into clinical studies as an antihypertensive agent.[4] Recently a synthesis of a related 2,2-bis(trifluoromethyl benzopyran PCO was also reported.[5] Thus we were prompted to reveal some of our own work in this area, specifically a series of highly potent fluoroalkyl benzoxazine pyridine-N-oxides as exemplified by **4**. This series highlights a maneuver for increasing potency, which may have more widespread generality in other related potassium channel openers such as the benzopyrans and related compounds, namely the incorporation of difluoromethyl or trifluoromethyl groups at the 2- position in these PCOs..



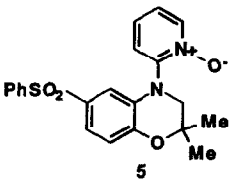
3



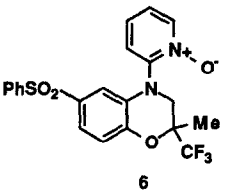
4

Compound	IC_{50} (nM)[6]	
	G.P. Detrusor	G.P. Portal vein
1	570±70	20±4
3	74.0±8.0	not tested
4	7.0 ± 1.0	0.60 ±0.09

Table 1.



5



6

Compound	IC_{50} (μM)
	Detrusor strip
5	4.1±0.9
6 (±)	0.54±0.1
7 (6 (S)(-))	0.28±0.05
8 (6 (R)(+))	0.68±0.08

Table 2.

The fluoroalkyl benzoxazine pyridine-N-oxide series were designed with the help of a cromakalim crystal receptor model.[7] In this analysis the pyridine-N-oxide accesses the same site as the pyrrolidinone in cromakalim, with both units functioning as H-bond acceptors. The dimethyl and trifluoromethyl methyl moieties fit into a lipophilic site The receptor model has suggested how structures such as **4**, cromakalim, and the anilide tertiary carbinol series could bind to the same PCO receptor site.[7]

We have also prepared the 2-trifluoromethyl-2-methyl analog (**6**), as well as the enantiomers of this compound, and have found a relatively small separation in the activity of the two enantiomers, with the S isomer being the most potent.[8] This result is of interest in light of Jones's results with the benzopyran PCOs where the 3- position chirality was of much greater significance to activity than the 4- position.[9] Inversion of chirality at the 2- position of **7** was expected to lead to a larger separation than observed, based on our results with the anilide tertiary carbinol series.[10]

The potassium channel opener activity of members of this series was characterized as follows. Thus 0.233μM of **4** increased the maximum ^{86}Rb (a K^+ surrogate) efflux rate from guinea pig detrusor by 40.5 ± 2.0% and this effect was 78% blocked by 30μM glibenclamide (30μM cromakalim caused a 47.2 ±11.6% increase). Against a 80mM K^+ challenge 30μM **6** did not relax detrusor tissue by 50%. In a spontaneously hypertensive rat model we have found that **4** is a very potent hypotensive agent showing significant and sustained lowering of blood pressure when dosed orally at 5 μg/kg (by 35mmHg (25%)). The effects lasted for around 8 -10 hours after dosing.

In summary we report the discovery of a novel series of highly potent potassium channel openers. Compound **4** was found to be a potent orally active antihypertensive agent in the spontaneously hypertensive rat.

References and Notes

1. Gopalakrishnan, M.; Janis, R. A.; Triggle, D. J. ATP-Sensitive K^+ Channels: Pharmacological Properties, Regulation, and Therapeutic Potential. *Drug. Development Research*, **1993**, *28*, 95.
2. Hamilton, T. C.; Weir, S. W.; Weston, A. H. Comparison Of The Effects Of Brl34915 And Verapamil On Electrical And Mechanical Activity In Rat Portal Vein. *Br. J. Pharmacol.* **1986**, *88*, 103.
3. Southerton, J. S.; Weston, A. H.; Bray, K. M.; Newgreen, D. T.; Taylor, S. G. The Potassium Channel Opening Action Of Pinacidil; Studies Using Biochemical, Ion Flux And Microelctrode Techniques. *Arch. Pharmacol.* **1988**, *338*, 310.
4. Matsumoto Y.; Tsuzuki, R.; Matsuhisa, A.; Takayama, K.; Yoden, T.; Uchida, W.; Asano, M.; Fujita, S.; Yanagisawa, I.; Fujikura, T. Potassium Channel Activators: Synthesis And SAR Studies Of Novel 1,4-Benzoxazine Derivatives, *Abstr. Pap. Am. Chem. Soc.* **1991**, *202*, (1-2), M99.
5. Fenwick, A. E. The Synthesis of 2,2-bis(trifluoromethyl)benzopyran Derivatives: A New Route to an Important Class of Potassium Channel Activators *Tetrahedron Letts.* **1993**, *34*, 1815.
6. Relaxation was measured either using a 15mM KCl contracted strip (Guinea-pig detrusor) or using spontaneous 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.
7. Russell, K.; Masek, B. Manuscipt in preparation
8. The synthesis of this series of compounds will be described in a forthcoming full paper.
9. Attwood, M. R.; Brown, B. S.; Dunsdon, R. M.; Hurst D. N.; Jones, P. S.; Kay, P. B. Synthesis Of Homochiral Potassium Channel Openers: Role Of The Benzopyranyl 3-Hydroxy Group In Cromakalim And Pyridine N-Oxides In Determining The Biological Activity Of The Enantiomers. *Biomed. Chem. Letts.*, **1992**, *2*, 229.
10. See accompanying paper.