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SYNTHESIS OF 2,3,4a,11b-TETRAHYDRO-OXAZINO[2,3-*c*]BENZOPYRAN-9-CARBONITRILES AS ATP-SENSITIVE POTASSIUM CHANNEL OPENERS

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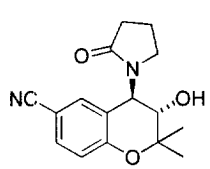
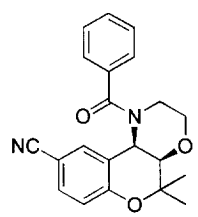
Abstract: A series of optically active tetrahydro-oxazino[2,3-*c*]benzopyran derivatives have been synthesized and evaluated for potassium channel opening activity. (4aR,11bR)-1-Benzoyl-5,5-dimethyl-2,3,4a,11b-tetrahydro-oxazino[2,3-*c*]benzopyran-9-carbonitrile ((-)-**11e**) was identified as a bladder-selective potassium channel opener ($IC_{50,\ bladder}$ = 8.15 μM, $IC_{50,\ portal\ vein}$ = 34.5 μM).

Since the discovery of cromakalim ((±)-**1**) as a typical ATP-sensitive potassium channel opener (PCO), a large number of 3,4-dihydro-2*H*-1-benzopyran derivatives have been synthesized and demonstrated to possess potent relaxant activity on blood vessels, cardiac muscle, and other smooth muscles.[1] These agents may find use in the treatment of a variety of diseases such as hypertension, asthma, ischemia, and urinary incontinence. However, their clinical utility may be limited largely due to a lack of tissue selectivity. In this paper, we would like to report the stereoselective synthesis of a series of tricyclic 2,3,4a,11b-tetrahydro-oxazino[2,3-*c*]benzopyran-9-carbonitriles (**5a-e**, **11a-e**, **13a-c**, and **14**),[2] which were designed on the basis of rigidization of the amide function and the 3-hydroxyl group in cromakalim. Within the series, the *cis* benzamide ((-)-**11e**) was found to be 4 times more potent on rat bladder detrusor muscle than on rat portal vein. Bladder-selective potassium channel openers, including series of anilide tertiary carbinols,[3] have only recently been reported.



(±)-**1**: Cromakalim
(-)-**1**: Lemakalim



(-)-**11e**

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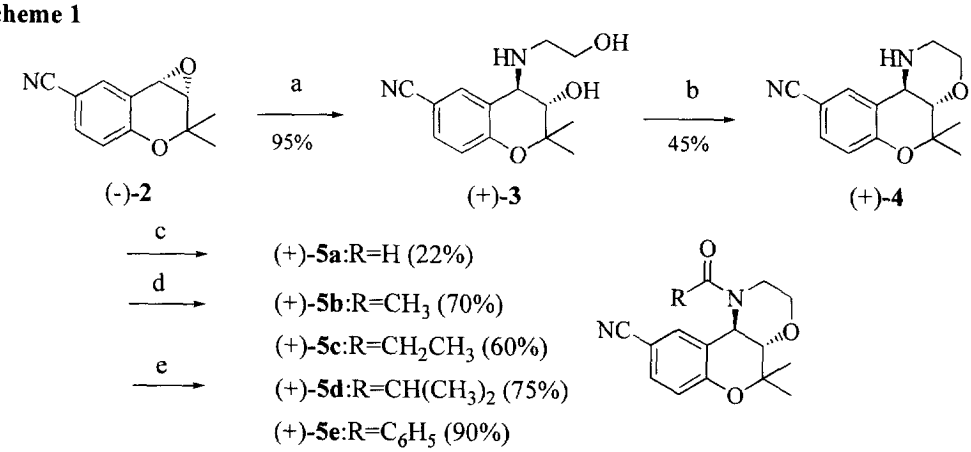
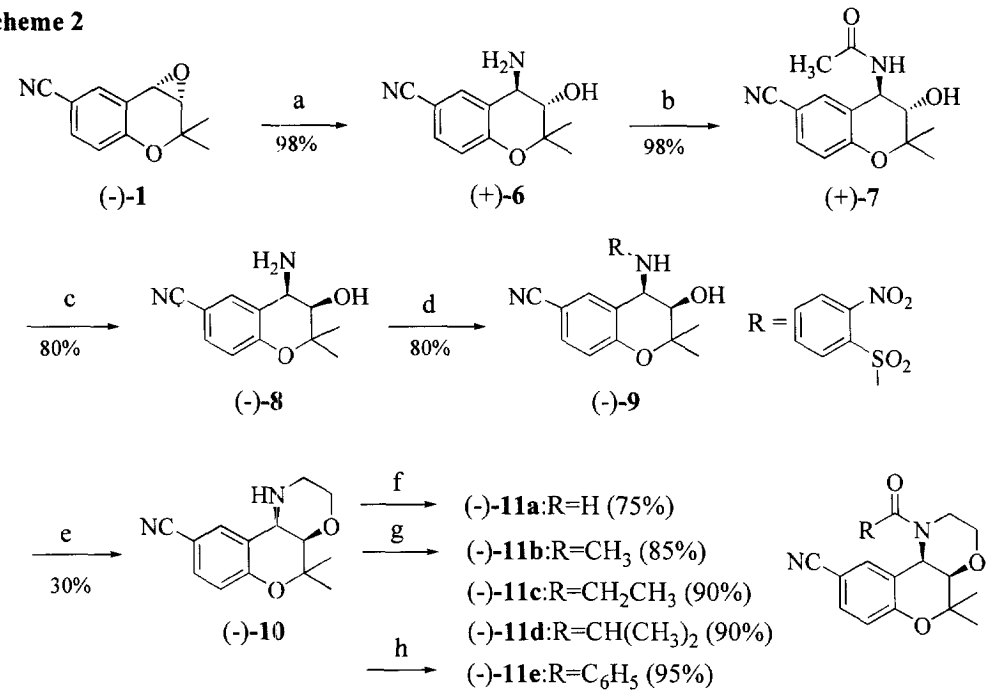
Compounds **5a-e**, which maintain the stereochemistry of lemakalim ((-)-**1**), the active enantiomer of cromakalim, were synthesized according to Scheme 1. The starting epoxide (-)-**2**, prepared from 6-cyano-2,2-dimethyl-2*H*-1-benzopyran via Mn(salen)-catalyzed asymmetric epoxidation,[4] was subjected to ring-cleavage by 2-aminoethanol to give the diol intermediate (+)-**3**. Treatment of **3** with Ph_3P/DEAD[5] resulted in the desired cyclization to form the tricyclic oxazino[2,3-*c*]benzopyran derivative (+)-**4**. Acylation of **4** under appropriate conditions as shown then provided the target compounds (+)-**5a-e**. The *cis*-isomers of **5a-e**, namely (-)-**11a-e**, were also prepared in a stereoselective fashion as shown in Scheme 2. The key steps are the inversion of the 3-OH function in amide-alcohol (+)-**7** effected by DAST[6] and the protection of the amino group in the resultant *cis*-aminoalcohol **8** as an *o*-nitrophenylsulfonamide.[7] The sulfonamide **9** then underwent the desired double alkylation with 1-bromo-2-chloroethane, albiet in low yield (30%), followed by deprotection to form the *cis*-oxazino[2,3-*c*]benzopyran derivative (-)-**10**. Acylation of **10** as described provided the *cis*-tetrahydro-oxazino[2,3-*c*]benzopyran derivatives (-)-**11a-e**. 2-Oxo-3*H*,5*H*-oxazino[2,3-*c*]benzopyran derivatives (-)-**13a** and (-)-**13b**, whose carbonyl groups are located within the tricyclic ring system at position 2, were also prepared. The starting *trans*-aminoalcohol (+)-**6** was treated with chloroacetyl chloride to give amide (+)-**12**, which underwent intramolecular O-alkylation to provide the target compound (+)-**13a**. Compound **13a** was treated with CH_3I/NaH to give the methyl analog (+)-**13b**. Interestingly, if an excess of NaH was used in the above methylation reaction, (+)-**13b** isomerized to the more stable *cis* isomer (-)-**14**. (Scheme 3) The N-benzyl analog **13c** was similarly prepared in racemic form from racemic epoxide (±)-**2**. The structure assignment of target compounds[8] is supported by X-ray crystal structure analysis, as represented by **5b**, **11b**, and **13b**. (Figure 1)

Scheme 1



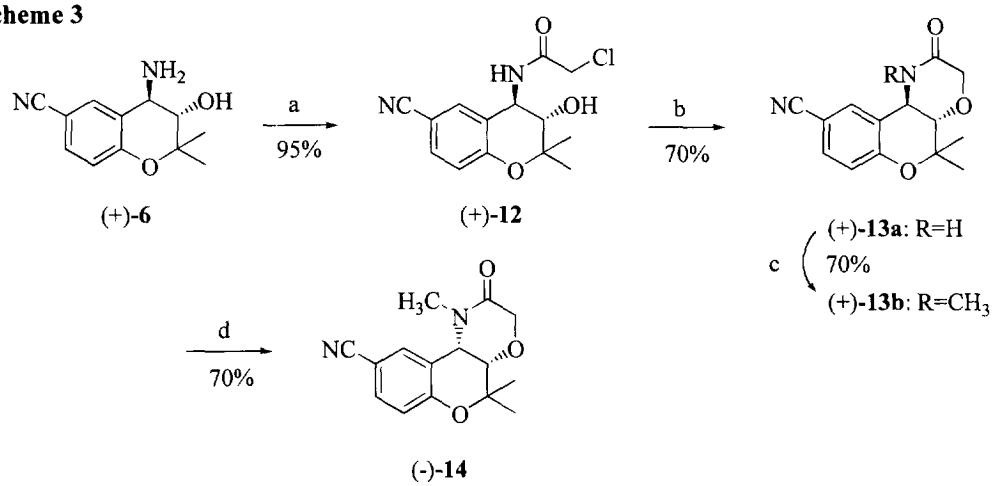
Reagents: (a) $H_2NCH_2CH_2OH$, THF, reflux. (b) Ph_3P, DEAD, THF,rt. (c) HCO_2COCH_3, pyridine, THF, -70°C to rt. (d) $(RCO)_2O$, pyridine, rt. (e) RCOCl, Et_3N, THF, rt.

Scheme 2



Reagents: (a) NH_3(30%), THF/EtOH= 1:1. (b) CH_3COCl, Et_3N, THF. (c) i. DAST, CH_2Cl_2; ii. 6NHCl, CH_3CN, reflux. (d) 2-nitrobenzenesulfonyl chloride, Et_3N, THF. (e) i. $BrCH_2CH_2Cl$, K_2CO_3, DMF, 70℃; ii. PhSH, K_2CO_3, DMF. (f) HCO_2COCH_3, pyridine, THF, -70℃. (g) $(RCO)_2O$, pyridine, rt. (h) PhCOCl, Et_3N, THF, rt.

Scheme 3



Reagents: (a) $ClCOCH_2Cl$, Et_3N, THF, 0℃. (b) NaH, $PhCH_3$-THF, 0℃. (c) CH_3I, NaH (1.1eq.), DMF, 0℃. (d) NaH (1eq.), DMF, rt.

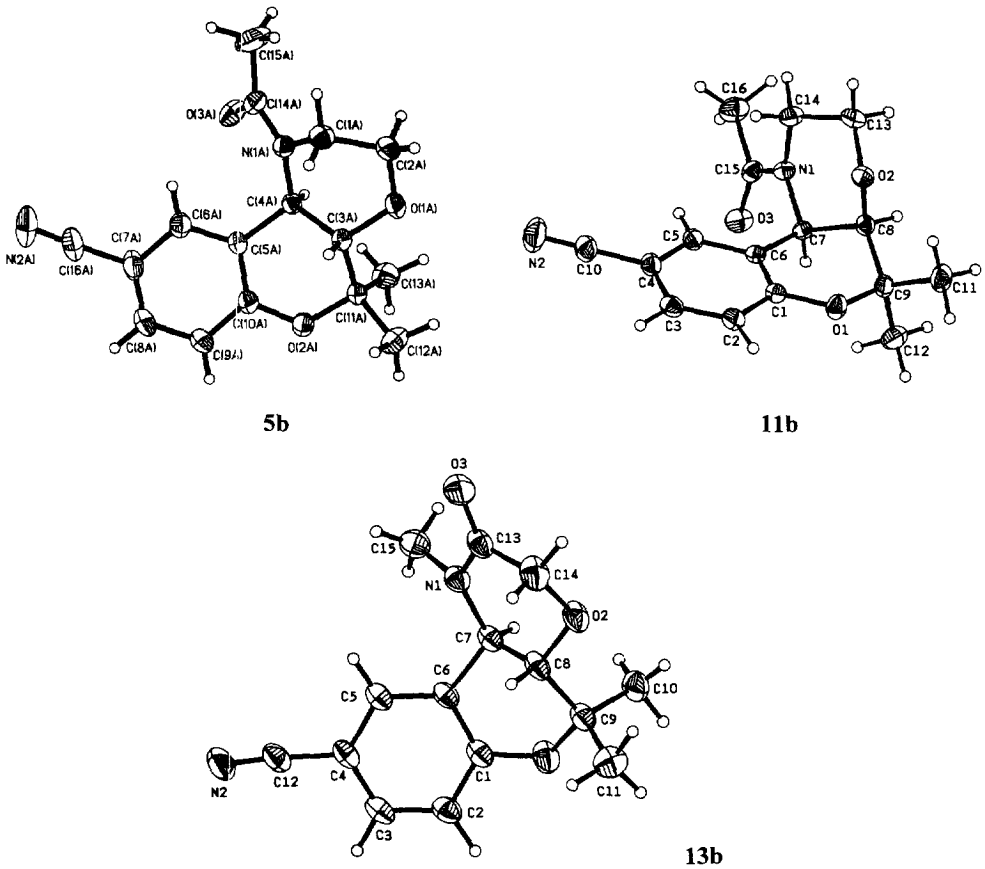
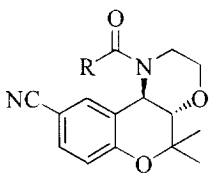


Figure 1. X-ray Crystal Structures of **5b**, **11b**, and **13b**

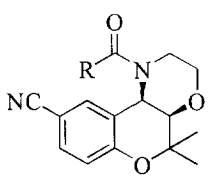
The PCO activity of the target compounds were evaluated *in vitro* with preparations of spontaneously contracting rat portal vein and KCl-stimulated rat detrusor strip based on literature procedures.[9] (Table 1) Most compounds tested, except **5a**, **5e**, **13a**, and **13c**, demonstrated significant relaxant activity on both rat portal vein and detrusor strip. The compounds are less potent than lemakalim. However, the observed relaxant activity was antagonized by the potassium channel inhibitor glibenclamide, indicating the direct involvement of potassium channels. Compounds **5a**, **5e**, **13a**, and **13c** showed weak enhancement activity on the portal vein, while maintaining weak relaxant activity on the detrusor. Within the 2-oxo series, only the methyl analogs **13b** and **14** showed relaxant activity on the portal vein. In general, the *cis* isomers (**11**) are more potent than the *trans* isomers (**5**), in contrast to the earlier finding that the (3R,4R)-*cis* isomer of lemakalim is 50 times weaker than lemakalim itself.[10] It is noteworthy that the *cis*-isomer **14**, which has a reversed configuration at C-11b as compared to that of the corresponding C-4 in lemakalim, is more potent than the (4aS,11bR)-*trans*

isomer **13b**. Among all the compounds synthesized, *cis*-benzamide **11e** is the most interesting, which showed the highest potency (IC_{50}, 8.15 μM) and selectivity (IC_{50} ratio, 4.2) on rat detrusor muscle and may serve as a lead compound for the discovery of clinically useful bladder-selective potassium channel openers. Further SAR study based on the above findings is currently in progress.

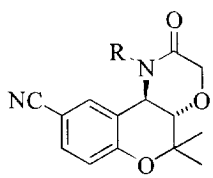
Table 1. Mechanoinhibitory Activity of 2,3,4a,11b-Tetrahydro-oxazino[2,3-*c*]benzopyran-9-carbonitriles on Rat Portal Vein and Rat Detrusor Strips[a]



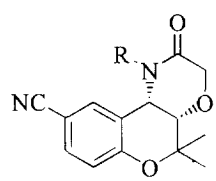
(+)-**5a-e**



(-)-**11a-e**



(+)-**13a,b**
(±)-**13c**



(-)-**14**

			IC_{50} (μM)			IC_{50}(μM) in the presence of Glibenclamide[b]	
compd	R	$[\alpha]_D$	portal vein[c]	detrusor[d]	IC_{50} ratio[e]	portal vein	detrusor
(+)-5a	H	+79.8	+[f]	152±28.4	—	ND[g]	158
(+)-5b	Me	+33.3	5.9±2.1	70.1±24.2	0.08	79.3	153
(+)-5c	Et	+24.6	64.9±10.6	47.2±18.1	1.38	92.6	318
(+)-5d	i-Pr	+56.9	127±12.3	104±8.7	1.22	ND	244
(+)-5e	Ph	+53.9	+	66±20	—	ND	123
(-)-11a	H	-125	62.8±18	51.8±17.6	1.21	117	279
(-)-11b	Me	-244	2.7±1.0	8.8±3.1	0.31	60.9	53.2
(-)-11c	Et	-310	20.1±8.9	51.8±3.06	0.39	52.6	141
(-)-11d	i-Pr	-155	18.4±2.5	56.4±5.2	0.33	58.9	268
(-)-11e	Ph	-114	34.5±0.71	8.15±1.9	4.23	45.5	32.8
(+)-13a	H	+150	+	53.1±14	—	ND	56.3
(+)-13b	Me	+85.7	50.2±16	43.8±7.2	1.15	72.8	79.5
(±)-13c	Bn	—	+	68.2±14.5	—	ND	130
(-)-14	Me	-185	26.2±5.6	65.7±18.5	0.4	28.3	129
lemakalim			0.13±0.08	0.82±0.2	0.16	4.9	8.7

[a]Data represents the mean of three experiments each performed in duplicate. [b]1 μM. [c]spontaneously contracting rat portal vein. [d]isolated rat detrusor strips exposed to extracellular KCl(20 μM). [e]$IC_{50,portal\ vein}/IC_{50,bladder}$. [f]The "+" sign indicates enhancement of the spontaneous contraction. [g]ND: not determined.

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References and Notes

1. For recent reviews on potassium channel openers, see: (a) Poyser, R. H.; Hamilton, T. C. *Drugs of the Future* **1994**, *19*, 39. (b) Empfield, J. R.; Russell, K. *Annu. Rep. Med. Chem.* **1996**, *30*, 81. (c) Pirotte, B.; Fontaine, J.; Lebrun, P. *Curr. Med. Chem.* **1995**, *2*, 573. (d) Atwal, K. S. *Curr. Med. Chem.* **1996**, *3*, 227. (e) *Potassium Channels and their Modulators: From Synthesis to Clinical Experience*; Evans, J. M.; Hamilton, T. C.; Longman, S. D.; Stemp, G., Eds; Taylor & Francis, 1996.
2. All target compounds, except **13c**, were prepared in optically active forms with absolute stereochemistry shown. Compound **13c** is racemic with relative stereochemistry shown.
3. Grant, T.; Frank, C. A.; Kau, S. T.; McLaren, F. M.; Ohnmacht, C. J.; Russell, K.; Shapiro, H. S.; Trivedi, S. *Bioorg. Med. Chem. Lett.* **1993**, *12*, 2723. (b) Grant, T. L.; Ohnmacht, C. J.; Howe, B. B. *TIPS* **1994**, *15*, 402. (c) Empfield, J. R.; Mayhugh, D.; Ohnmacht, C. J.; Frank, C. A.; Grant, T.; Li, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 775.
4. Lee, N. H.; Muci, A. R.; Jacobson, E. C. *Tetrahedron Lett.* **1991**, *32*, 5055.
5. Mitsunobu, O. *Synthesis* **1981**, 1.
6. Houge-Frydrych, C. S. V.; Pinto, I. L. *Tetrahedron Lett.* **1989**, *30*, 3349.
7. Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
8. All new compounds gave satisfactory elemental analysis and/or spectroscopic data.
9. Zografos, P.; Li, J. H.; Kau, S. T. *Pharmacol.* **1992**, *45*, 216.
10. Quast, U.; Villhauer, E. B. *Eur. J. Pharmacol.* **1993**, *245*, 165.