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4-SULFONAMIDOANILIDE TERTIARY CARBINOLS: A NOVEL SERIES OF POTASSIUM CHANNEL OPENERS

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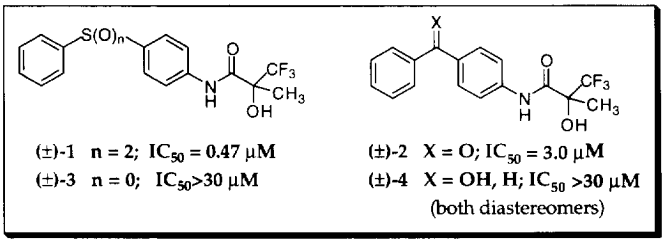
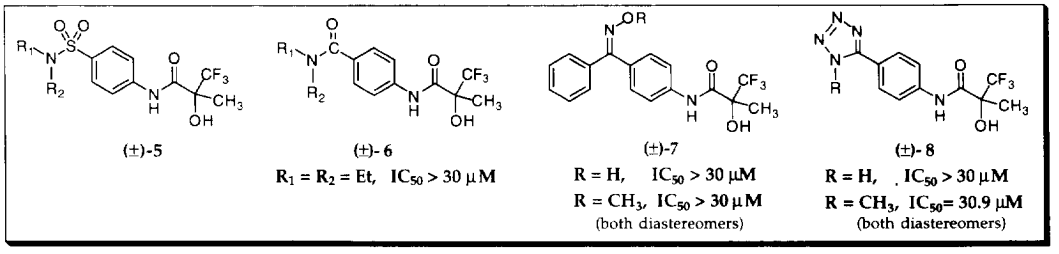
Abstract: Sulfonamides are viable replacements for the phenylsulfonyl and benzoyl moieties initially described for the anilide tertiary carbinol series of K_{ATP} potassium channel openers. The SAR of this new series and the synthetic chemistry employed to generate its members are described. © 1997 Elsevier Science Ltd.

Potassium channel openers (PCOs) have potential for many therapeutic indications.[1] During our search for an agent for the treatment of urge urinary incontinence we focused on ATP-dependent (K_{ATP}) PCOs.[2] We have recently reported initial results from a novel series of PCOs, namely the anilide tertiary carbinols.[3] Two representative examples include **1** and **2**, the phenylsulfone and benzophenone analogs, respectively. Herein we report the structure-activity relationships (SAR) of sulfonamide replacements in the western region of this series.



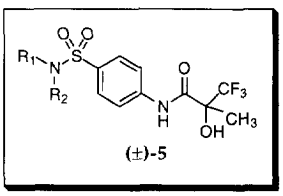
We previously reported[4] the presence of large substituents on the anilide ring as a requirement to avoid antiandrogen activity with this template. A further necessary, but not sufficient, structural requirement for this series of PCOs is that a strong electron withdrawing para substituent be present on the anilide ring, as exists in **1** and **2**. Removal of the electron withdrawing group inactivates this series as exemplified by the comparison of **3** and **4** to **1** and **2**, respectively. The phenylsulfone and benzophenone derivatives **1** and **2** are severely sterically restricted at the para position of the western aryl ring tolerating only substitution by fluorine.



Molecular modeling[5] suggested that the western aryl rings of **1** and **2** do not occupy the same site of the receptor, leading us to postulate that other moieties may be tolerated within this series. To explore this possibility, we investigated other large electron withdrawing groups as 4-aryl substituents, such as sulfonamides (**5**), amides (**6**),

oximes (**7**), and tetrazoles (**8**). Each of these moieties was envisioned to possess the electronic requirements necessary to maintain PCO activity. The sulfonamide and amide analogs were particularly attractive since they permit a more comprehensive exploration of space and offer the greatest variation of physical properties. Surprisingly, only the sulfonamide derivatives possess significant in vitro PCO activity. This series was therefore further evaluated; the in vitro[6] activity for this class of compounds is shown in Table I. This data clearly shows that sulfonamides are viable replacements for the phenylsulfonyl and benzoyl moieties within this series of tertiary carbinols. In fact, equal or greater biological potency can be achieved with this series than seen with **1** and **2**. Disubstituted analogs are in general more potent than the mono or unsubstituted sulfonamides unless they possess unfavorable steric bulk (e.g., **5e**, **5f**, and **5i**). Given the above mentioned steric limitations of the western aryl ring of **1** and **2**, the significant activity of **5h** suggests that the N-substituents of the sulfonamide derivatives access a different area within the receptor.

Table I. PCO In Vitro Activity of Sulfonamide Tertiary Carbinols

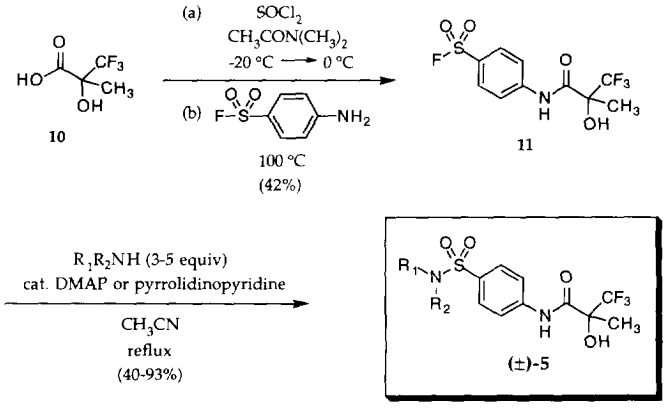


(±)-5

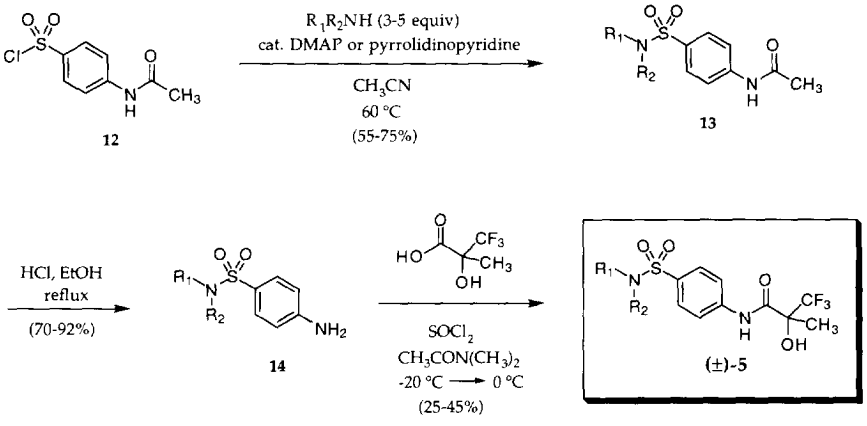
Compound #	R_1	R_2	IC_{50} (μM)
a	H	H	12.8 ± 2.4
b	Me	Me	0.48 ± 0.09
c	Et	Et	0.81 ± 0.16
d	n-Pr	n-Pr	6.44 ± 1.70
e	s-Bu	s-Bu	>30
f	i-Bu	i-Bu	>30
g	Ph	H	>30
h	Ph	Me	1.97 ± 0.54
i	Ph	Ph	>30
j	$-(CH_2)_4-$		0.88 ± 0.27
k	$-(CH_2)_5-$		9.25 ± 1.41
l	$-(CH_2)_2-O-(CH_2)_2-$		5.85 ± 0.84
m	$-(CH_2)_2-NH-(CH_2)_2-$		>30
n	$-(CH_2)_2-S-(CH_2)_2-$		4.58 ± 0.75
9	**Cromakalim**		0.5-0.9

Two synthetic approaches were employed to prepare the above mentioned sulfonamide tertiary carbinols. These methods differ in the ordering of amide and sulfonamide couplings. Method A (Scheme 1) involves amide formation via coupling of sulfanilyl fluoride with activated 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid[7] prior to sulfonamide generation. The sulfonamides were then prepared by nucleophilic addition of amines to the sulfonyl fluoride moiety. This is the preferred route as the sulfonyl fluoride intermediate **11** can be stored and converted in one step to the desired sulfonamide **5**. However, this route was found to be useful only for the more reactive amines. For the more hindered or less nucleophilic amines an alternative approach, Method B (Scheme 2) was employed. This route employs the more reactive sulfonyl chloride **12**, to prepare the sulfonamide moiety. N-Deacetylation followed by coupling with activated 3,3,3-trifluoro-2-hydroxy-2-methylpropanoic acid provided **5** in modest to good yields. Alternatively, **14** could be prepared directly from sulfanilic acid (**15**) as reported by Bieber and Kane[8] and outlined in Scheme 3 (Method C). The method and overall yields for **5a-n** are shown in Table 2.

Scheme 1. Preparation of the Tertiary Carbinol Sulfonamides (±)-**5**: Method A



Scheme 2. Preparation of the Tertiary Carbinol Sulfonamides (±)-**5**: Method B



Scheme 3. Preparation of the Tertiary Carbinol Sulfonamides (±)-**5**: Method C

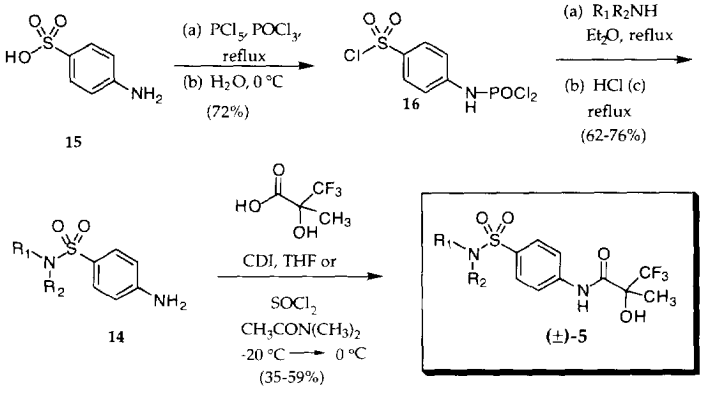


Table 2. Yields for the Preparation of Sulfonamides (±)-**5**

Compound 5	R_1	R_2	Method	Overall % Yield[a]
a	H	H	**B**	**47**
b	Me	Me	**B**	**20**
c	Et	Et	**C**	**22**[b]
d	n-Pr	n-Pr	**A**	**15**
e	s-Bu	s-Bu	**B**	**10**
f	i-Bu	i-Bu	**B**	**15**
g	Ph	H	**B**	**24**
h	Ph	Me	**C**	**45**[b]
i	Ph	Ph	**B**	**5**
j	$-(CH_2)_4-$		**A**	**39**
k	$-(CH_2)_5-$		**A**	**37**
l	$-(CH_2)_2-O-(CH_2)_2-$		**A**	**17**
m	$-(CH_2)_2-NH-(CH_2)_2-$		**A**	**22**
n	$-(CH_2)_2-S-(CH_2)_2-$		**A**	**32**

[a]Yields of isolated and purified products. Satisfactory microanalysis was obtained on all products.
[b]Yield from intermediate **16**

In summary, the SAR of the tertiary carbinol series of K_{ATP} PCOs requires that a para electron withdrawing substituent be present on the anilide aryl ring. This is a necessary but not sufficient requirement as amides (**6**), oximes (**7**), and tetrazoles (**8**) have greatly diminished activity. Sulfonamides, however, are viable replacements for the western phenylsulfonyl and benzoyl moieties initially reported for this series of compounds. Herein we have reported the in vitro activity and described synthetic routes to this novel series of K_{ATP} PCOs.

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5. Molecular mechanics computations were performed using the AESOP force field and ENIGMA. AESOP is an in house molecular mechanics program (Masek, B., Zeneca, Inc., 1800 Concord Pike, Wilmington, DE 19897) derived from BIGSTRN-3(QCPE 514) (Nachbar, R., Jr.; Mislow, K. *QCPE Bull.* **1986**, *6*, 96). ENIGMA is an in house molecular graphics program (Zeneca, Inc., 1800 Concord Pike, Wilmington, DE 19897).
6. In vitro activity was measured via relaxation of drug candidates on depolarized (15 mM KCl) guinea pig detrusor strips. For details see Zografos, P.; Li, J. H.; Kau, S. K. *Pharmacology* **1992**, *45*, 216.
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