Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters 17 (2007) 2849–2853
Bioorganic & Medicinal Chemistry Letters

Aryl sulfonamido indane inhibitors of the Kv1.5 ion channel

Michael F. Gross,[a] Serge Beaudoin,[a,*] Grant McNaughton-Smith,[a] George S. Amato,[a] Neil A. Castle,[a] Christine Huang,[b] Anruo Zou[a] and Weifeng Yu[a]

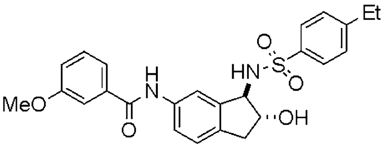
[a] *Icagen Inc., PO Box 14487, Research Triangle Park, NC 27709, USA*
[b] *Bristol-Myers Squibb Pharmaceutical Research Institute, Pennington, NJ 08534, USA*

Received 23 January 2007; revised 16 February 2007; accepted 21 February 2007

Abstract—A collection of aryl sulfonamido indanes based on the lead compound **1** was synthesized and evaluated for Kv1.5 inhibitory activity. Kv1.5 inhibitors have the potential to be atrium-selective agents for treatment of atrial fibrillation. (1*R*,2*R*)-**1** has an IC_{50} of 0.033 μM against Kv1.5 and is selective against other cardiac ion channels, including hERG.

Atrial fibrillation (AF) is one of the most common forms of cardiac disease encountered in clinical practice. Currently, over two million people in the United States are affected by this serious cardiac arrhythmia.[1] Although AF is typically not a fatal condition, inefficient emptying of the atrium leads to concomitant patient risks, such as thrombogenesis and stroke.[2] AF is a major public health concern and there is a growing medical need to reduce the occurrence of AF with drugs that lack the ventricular proarrhythmic side effects (e.g., torsades de pointes) associated with currently used pharmacological therapies.[3]

In humans, the delayed rectifier potassium current termed I_{Kur} has been shown to play an important role in atrial muscle action potential repolarization.[4] In contrast to other potassium currents present in the heart such as I_{Ks} and I_{Kr}, I_{Kur} is functionally expressed only in the atrium.[5] The I_{Kur} current is conducted by the voltage-gated potassium channel encoded by Kv1.5.[6] Thus, an inhibitor of Kv1.5 would be expected to prolong the action potential repolarization in the atrium but not in the ventricle. Drugs that selectively block this ion channel should increase atrial action potential duration and prevent and/or terminate AF without the risk of ventricular effects leading to arrhythmogenesis.



1

Figure 1. Structure of aryl sulfonamido indane Kv1.5 inhibitor.

Herein, we report a new class of Kv1.5 inhibitors based on the indane scaffold (Fig. 1).[7] In this study, amido regioisomers and scaffold variations were probed in an attempt to define the Kv1.5 pharmacophore.

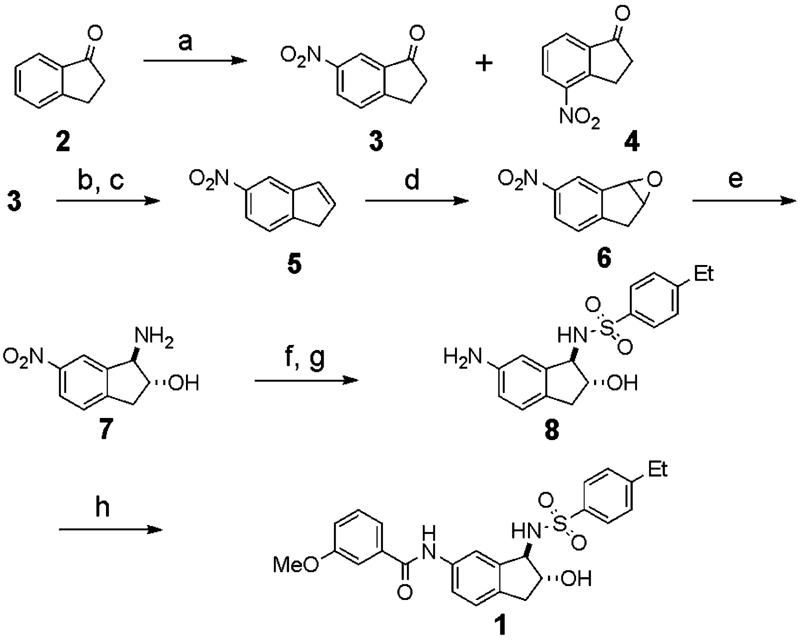
The preparation of aryl sulfonamido indane **1** is presented in Scheme 1. Nitration of 1-indanone **2** afforded 6-nitro-1-indanone **3** and 4-nitro-1-indanone **4** in a 3:1 ratio following column chromatography on silica gel. Ketone reduction of **3** followed by dehydration gave the indene **5**. Treatment with *m*-CPBA to furnish epoxide **6** and subsequent ring opening with ammonium hydroxide provided the racemic *trans*-amino alcohol **7**. Sulfonylation of **7** with 4-ethylphenylsulfonyl chloride and reduction gave aromatic amine **8**. Several methods were used to reduce the nitro group. We found the use of $SnCl_2$–$2H_2O$ or $NaBH_4$ with catalytic $NiCl_2$ was generally preferred over hydrogenation using Pd/C. Coupling of **8** with *m*-anisoyl chloride provided **1**.

The 1,4-, 1,5-, and 1,7-regioisomers were synthesized to determine the optimal positioning of the amido group. Manipulation of **4** in a manner identical to that described in Scheme 1 provided the 1,4-amido regioisomer **9** (Scheme 2).

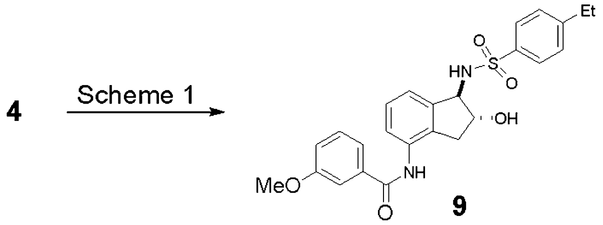
Keywords: Kv1.5 inhibitors; Atrial fibrillation.

* Corresponding author. E-mail: sbeaudoin@icagen.com

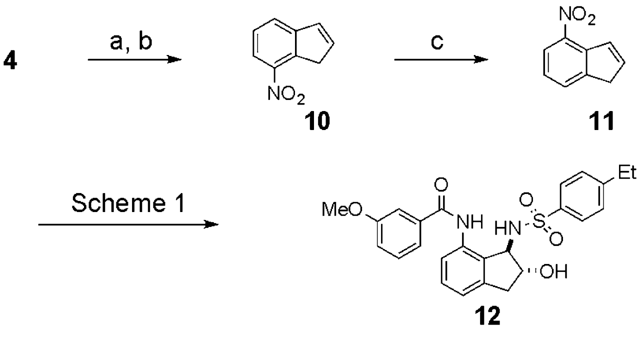
0960-894X/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2007.02.052



Scheme 1. Reagents: (a) KNO_3, concd H_2SO_4, 74%; (b) $NaBH_4$, MeOH, 99%; (c) TsOH, $PhCH_3$, 100%; (d) *m*-CPBA, CH_2Cl_2, 96%; (e) NH_4OH, 91%; (f) 4-Et-$PhSO_2Cl$, Et_3N, CH_2Cl_2, 83%; (g) $SnCl_2$–$2H_2O$, EtOH, 97%; (h) *m*-anisoyl chloride, Et_3N, CH_2Cl_2, 93%.



Scheme 2. Synthesis of 4-amido regioisomer **9**.



Scheme 3. Reagents: (a) $NaBH_4$, MeOH, 98%; (b) TsOH, toluene, 100%; (c) $RhCl_3$–H_2O, EtOH, 43%.

The 1,7-amido regioisomer **12** was also prepared starting from **4**. Ketone reduction and dehydration of **4** gave indene **10**. Isomerization of the olefin using $RhCl_3$ in refluxing ethanol afforded indene **11**, along with recovered **10**. Processing of **11** as described in Scheme 1 provided the 1,7-amido derivative **12** (Scheme 3).

The 1,5-amido regioisomer **17** was synthesized as described in Scheme 4 to complete the series. Nitration of indane (**13**) gave a 2:3 mixture of nitroindanes **14** and **15**.[8] Oxidation of this mixture using chromium trioxide provided a 3:3:1 mixture of nitroindanones **16**, **4**, and **3**. The desired 5-nitroindanone **16** was isolated by column chromatography. Further elaboration of **16** proceeded as before to provide the 1,5-amido regioisomer **17**.

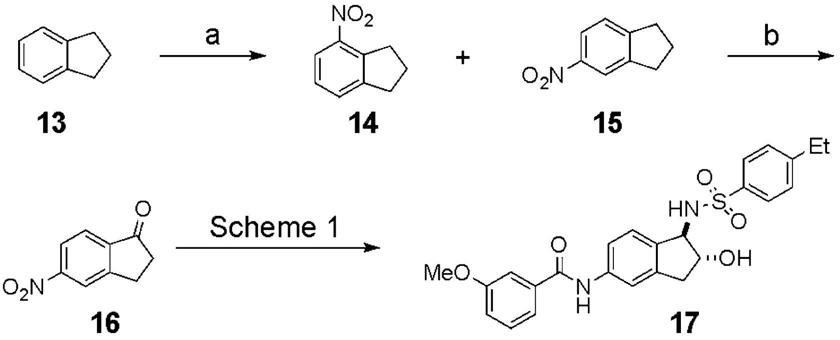
The des-amido indane **19** was prepared in order to determine the contribution of the amido functionality to Kv1.5 activity. Oxidation, ring opening, and sulfonylation of 1-indene **18** provided racemic **19** (Scheme 5).

We wanted to ascertain if the 2-hydroxy group interacted with the Kv1.5 channel protein. The racemic des-hydroxy indane **20** was prepared via amination of **3** followed by sulfonylation, nitro reduction, and acylation as described in Scheme 6.

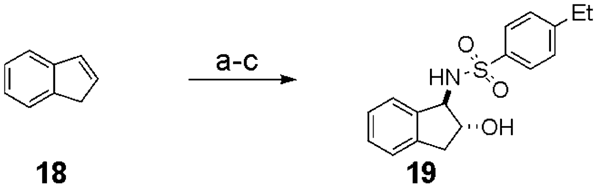
To further explore the SAR at the 2-position, the *cis*-amino alcohol **22** was prepared as outlined in Scheme 7. Treatment of indene oxide **6** with trifluoromethanesulfonic acid in acetonitrile provided racemic **21**.[9] This intermediate was carried forward as described in Scheme 1 to give **22**.

Scaffold variations were investigated (Fig. 2). The tetralin **23** and benzosuberone **24** were synthesized in a fashion identical to that illustrated for indane **1** (Scheme 1) starting from the appropriate commercially available precursors, 7-nitro-1-tetralone and 1-benzosuberone, respectively.

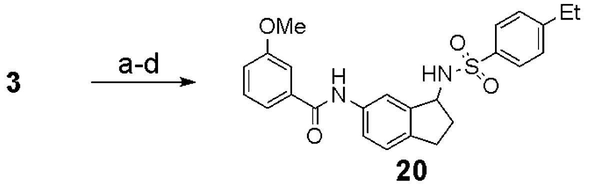
The benzyl sulfonamide **26** was prepared in order to determine whether conformational rigidity imposed by the indane scaffold was important for Kv1.5 activity. Sulfonylation of 3-nitrobenzyl amine **25**, nitro reduction and coupling with *m*-anisoyl chloride provided the desired acyclic product (Scheme 8).



Scheme 4. Reagents: (a) HNO_3, H_2SO_4, 37%; (b) CrO_3, AcOH, 3% of **16**.



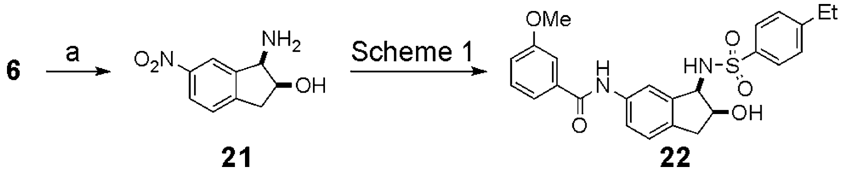
Scheme 5. Reagents: (a) *m*-CPBA, CH_2Cl_2, 93%; (b) NH_4OH, 85%; (c) 4-Et-$PhSO_2Cl$, NEt_3, CH_2Cl_2, 81%.



Scheme 6. Reagents: (a) NH_4OAc, $Na(CN)BH_3$, MeOH, 35%; (b) 4-Et-$PhSO_2Cl$, NEt_3, CH_2Cl_2, 88%; (c) $SnCl_2$–$2H_2O$, EtOH, 91%; (d) *m*-anisoyl chloride; NEt_3, CH_2Cl_2, 92%.

Finally, we wanted to compare the ability of enantiomers (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1** to inhibit the Kv1.5 channel. (1*R*,2*R*)-**1** was prepared via Jacobsen asymmetric epoxidation of indene **5**.[10] Under these conditions, the epoxide (1*S*,2*R*)-**6** was obtained in 70% ee.[11] The stereochemistry was assigned based on literature precedent suggesting the major isomer expected from the (*S*,*S*)-salen catalyst would be the (1*S*,2*R*) isomer.[10] (1*S*,2*R*)-**6** was carried on to give the amino alcohol (1*R*,2*R*)-**7**, then processed as described in Scheme 1 to ultimately provide (1*R*,2*R*)-1 in 95% ee, after recrystallization from iPrOH/hexane (Scheme 9). In order to obtain both the (1*R*,2*R*)-**1** and (1*S*,2*S*)-**1** expeditiously, the racemate was subjected to preparative-scale chiral HPLC chromatography to provide each enantiomer in >98% ee.

Compounds were tested for inhibition of potassium current in Ltk$^-$ or mouse fibroblast L929 cells expressing human Kv1.5 using patch-clamp electrophysiological (EP) techniques.[12] The inhibitory activities of the compounds examined in this study are summarized in Table 1.



Scheme 7. Reagents: (a) CF_3SO_3H, CH_3CN, 64%.

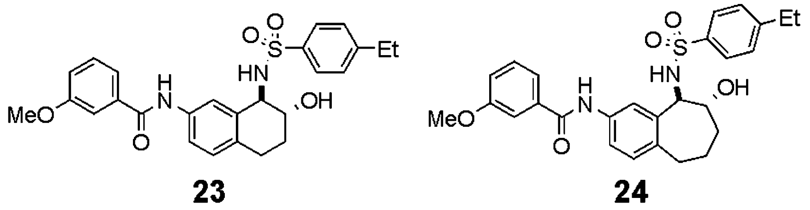
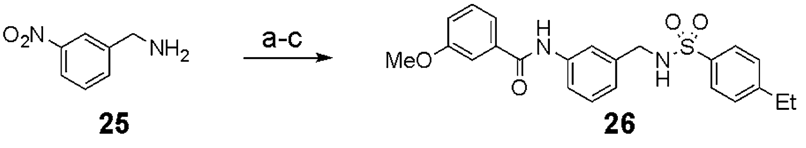
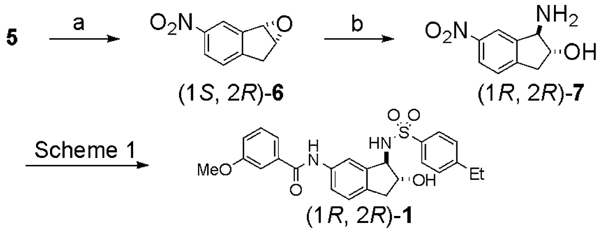


Figure 2. Tetralin and Benzosuberone Kv1.5 inhibitors.



Scheme 8. Reagents: (a) 4-Et-$PhSO_2Cl$, NEt_3, CH_2Cl_2, 99%; (b) $SnCl_2$–$2H_2O$, EtOH, 99%; (c) *m*-anisoyl chloride; NEt_3, CH_2Cl_2, 95%.



Scheme 9. Reagents: (a) (*S*,*S*)-Mn-salen catalyst, PPNO, NaOCl, 0.05 M NaH_2PO_4, CH_2Cl_2, 71% yield, 70% ee; (b) NH_4OH, 90%.

Table 1. Kv1.5 Inhibitory activity

Compound	IC_{50} (μM) or inhibition at 1 μM[a]
1	0.16
(1*R*,2*R*)-**1**	0.033
(1*S*,2*S*)-**1**	0.76
8	2 ± 2%
9	17 ± 1%
12	0.88
17	24 ± 3%
19	3 ± 1%
20	0.15
22	0.30
23	0.44
24	0.20
26	0.24

[a] Inhibition values are means of at least two experiments ± SEM.

All four of the possible amido regioisomers were examined in this study. The 1,7-isomer **12** retained a reasonable level of Kv1.5 activity, whereas the 1,4- and 1,5-isomers (**9** and **17**, respectively) were less potent having IC_{50} values >1 μM. Clearly, the 1,6-isomer **1** arranged the sulfonamido and amido groups in the most preferred orientation. Removal of the amido functionality was not tolerated (see **8** and **19**).

The des-hydroxy indane **20** and *trans* indane **1** were essentially equipotent. The *cis* indane **22** was slightly less potent (approximately 2-fold). Combined, these results suggest that the 2-hydroxy group does not participate in a critical binding interaction with the Kv1.5 channel protein. Removing the hydroxyl group from the indane template, however, resulted in a substantial loss of aqueous solubility (Table 2).

Of the bicyclic scaffold modifications that were explored, the indane series retained the highest level of Kv1.5 inhibitory activity. Nevertheless, the tetralin and benzosuberone aryl sulfonamido templates (**23** and **24**, respectively) have the potential to be optimized further to provide interesting Kv1.5 inhibitors.[14] It appeared that conformational constraint is not required for Kv1.5 activity based on potency of **26**. However, this compound suffered from the same solubility limitations as the des-hydroxy analog **20** (Table 2).

Table 2. Aqueous solubility of Kv1.5 inhibitors[13]

Compound	μg/mL
1	2.9
(1*R*,2*R*)-**1**	1.3
20	<0.1
26	0.8

The chirality of **1** significantly influenced Kv1.5 channel blockade: (1*R*,2*R*)-**1** was approximately 25 times more potent than (1*S*,2*S*)-**1**. Encouraged by this level of activity, the inhibitory effect of (1*R*,2*R*)-**1** was studied on other ion channels including a human cardiac potassium channel (hERG),[15] a human cardiac voltage-dependent sodium channel (hSCN5A),[16] and calcium channels found in a rat pituitary cell (GH3).[17] Compound (1*R*,2*R*)-**1** was found to be at least 300-fold selective, producing <50% inhibition at 10 μM versus all three of these ion channels (Table 3).

Satisfied with the in vitro profile of (1*R*,2*R*)-**1**, the pharmacokinetic (PK) properties were investigated in rat and dog. Despite favorable calculated (e.g., clog*P*, H-bond donors, H-bond acceptors, MW)[18] and measured (e.g., CACO-2 permeability of 1.9×10^{-5} cm/s) properties, we found that the oral bioavailability (*F*%) of (1*R*,2*R*)-**1** was low in both species. In addition, the intraarterial infusion (INF) half-life was short, particularly in rat (Table 4).

In an effort to understand why the oral bioavailability of (1*R*,2*R*)-**1** was so low, a separate PK experiment was performed using bile duct cannulated (BDC) rats. It was discovered that the INF dose was rapidly and extensively metabolized. Deacylation, *O*-dealkylation and hydroxylation to give metabolites **I**, **II**, and **III**, respectively, were predominant metabolic pathways (Fig. 3). It was not determined whether hydroxylation of the sulfonamido fragment occurred on the phenyl ring or on the ethyl substituent (**III**).

Thorough analysis of the oral (PO) dose in BDC rats revealed that most of (1*R*,2*R*)-**1** remained unabsorbed from the gastrointestinal tract. This was attributed largely to the poor aqueous solubility of (1*R*,2*R*)-**1** that was measured to be 1.3 μg/mL (Table 2).

Table 3. Cardiac ion channel selectivity of (1*R*,2*R*)-**1**

Ion channel	Inhibition at 10 μM[a]
hERG	37 ± 5%
hSCN5A	15 ± 4%
GH3 (Ca)	27 ± 4%

[a] Inhibition values are means of at least three EP experiments ± SEM.

Table 4. Pharmacokinetic parameters of (1*R*,2*R*)-**1**[a]

Parameter	Rat	Dog
F (%)	1 ± 0.6	5 ± 2
$t_{1/2}$ (h)	0.4 ± 0.01	1.5 ± 0.2
Clearance (mL/min/kg)	200	12
V_d (L/kg)	4	1.4

[a] Dose: 20 μmol/kg PO; 10 μmol/kg INF; vehicle: 1:1:1 PEG:EtOH:H_2O.

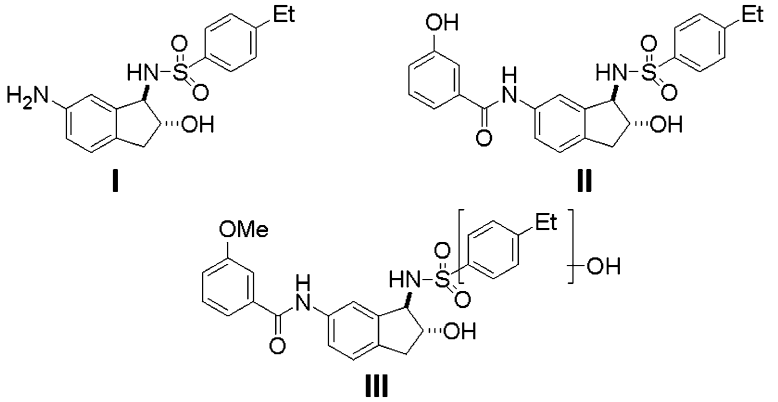


Figure 3. In vivo metabolites of (1*R*,2*R*)-**1**.

In summary, we investigated the Kv1.5 pharmacophoric elements of the aryl sulfonamido indane series. It was discovered that (1*R*,2*R*)-**1** is a potent Kv1.5 inhibitor with an IC_{50} of 0.033 μM. The selectivity of (1*R*,2*R*)-**1** versus other cardiac ion channels indicates this compound may have the potential for treating AF without the risk of unwanted ventricular effects. However, the unacceptable pharmacokinetic profile of (1*R*,2*R*)-**1** precludes its further development. In subsequent publications we will discuss our efforts to design Kv1.5 inhibitors having more desirable physiochemical and PK properties.

References and notes

1. (a) Page, R. L.; Roden, D. M. *Nat. Rev. Drug Disc.* **2005**, *4*, 889; (b) Lloyd-Jones, D. M.; Wang, T. J.; Leip, E. P.; Larson, M. G.; Levy, D.; Vasan, R. S.; D'Agostino, R. B.; Massaro, J. M.; Beiser, A.; Wolf, P. A.; Benjamin, E. J. *Circulation* **2004**, *110*, 1042.
2. Crystal, E.; Connolly, S. J. *Heart* **2004**, *90*, 813.
3. (a) Recanatini, M.; Poluzzi, E.; Masetti, M.; Cavalli, A.; De Ponti, F. *Med. Res. Rev.* **2005**, *25*, 133; (b) Clancy, E. E.; Kurokawa, J.; Tateyama, M.; Wehrens, X. H. T.; Kass, R. S. *Annu. Rev. Pharmacol. Toxicol.* **2003**, *43*, 441;; (c) Yang, T.; Snyders, D.; Roden, D. M. *J. Cardiovasc. Pharmcol.* **2001**, *38*, 737.
4. Nerbonne, J. M.; Kass, R. S. *Physiol. Rev.* **2005**, *85*, 1205.
5. Li, G.-R.; Feng, J.; Yue, L.; Carrier, M.; Nattel, S. *Circ. Res.* **1996**, *78*, 689.
6. Fedida, D.; Wible, B.; Wang, Z.; Fermini, B.; Faust, F.; Nattel, S.; Browm, A. M. *Circ. Res.* **1993**, *73*, 210.
7. Compounds in this letter were first disclosed in patent application WO9804521.
8. Markgraf, J. H.; Greeno, E. W.; Miller, M. D.; Zaks, W. J.; Lee, G. A. *Tetrahedron Lett.* **1983**, *24*, 241.
9. Senanayake, C. H.; DiMichele, L. M.; Liu, J.; Fredenburgh, L. E.; Ryan, K. M.; Roberst, F. E.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7615.
10. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
11. Enantiomeric excess (ee) was determined by chiral HPLC using a CHIRALPAK AS column.
12. Synders, D. J.; Tamkun, M. M.; Bennett, P. B. *J. Gen. Physiol.* **1993**, *101*, 513.
13. Aqueous solubility of the crystalline solids was determined in 50 mM phosphate-buffered saline at pH 6.8 using the shake-flask method and LC/MS/MS detection.
14. Gross, M. F.; Castle, N. A.; Zou, A.; Wickenden, A. D.; Yu, W.; Spear, K. L. *Bioorg. Med. Chem. Lett.* **2006**, in preparation.
15. Nerbonne, J. M. *J. Physiol.* **2000**, *525*, 285.
16. Gellens, M. E.; George, A. L.; Chen, L.; Chahine, M.; Horn, R.; Barchi, R. L.; Kallen, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 554.
17. Glassmeier, G.; Hauber, M.; Wulfsen, I.; Weinsberg, F.; Bauer, C. K.; Schwarz, J. R. *Pflugers Arch.* **2001**, *442*, 577.
18. Lipinski, C. A. *Adv. Drug Delivery Rev.* **2001**, *46*, 3.