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Aryl sulfonamido tetralin inhibitors of the Kv1.5 ion channel

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ABSTRACT

Aryl sulfonamido tetralins based on lead compound **2a** were synthesized and evaluated for Kv1.5 inhibitory activity. Several compounds having IC_{50} values less then 0.1 μM were identified. Kv1.5 inhibitors have the potential to be atrium-selective agents for the treatment of atrial fibrillation.

The need for safe and effective drugs to treat atrial fibrillation (AF) is growing. AF is a common cardiac rhythm abnormality that affects millions of people, particularly the elderly.[1] Projections suggest that as many as 5.6 million adults in the United States will be affected by AF by 2050.[2] AF can reduce cardiac performance and is a serious risk factor for stroke.[3]

Voltage-gated potassium channel blockers hold promise as therapeutic agents for the treatment of atrial AF. Several potassium channels including I_{Kr}, I_{Ks} and I_{Kur} play prominent roles in cardiac action potential repolarization.[4] Existing treatment options for atrial stabilization typically inhibit more then one of these potassium currents and inevitably influence atrial as well as ventricular refractoriness.[1a] I_{Kur} is not detected in ventricular cells which makes it is a particularly attractive molecular target for the treatment of AF.[5] In humans, the I_{Kur} current is conducted by the voltage-gated potassium channel encoded by Kv1.5.[6] Thus, selective blockade of Kv1.5 should prevent and/or terminate AF without the threat of ventricular side effects.

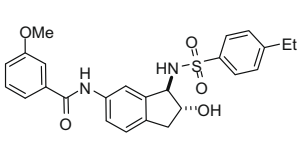
Our search for Kv1.5 inhibitors led to the identification of aryl sulfonamido indane **1**, a potent, selective potassium channel blocker.[7] Initial structure–activity relationship (SAR) discoveries established that Kv1.5 inhibitory activity was maintained upon expansion of the five-membered saturated ring (indane scaffold) to the six-membered ring (tetralin scaffold). In this communication we would like to report our SAR studies designed to optimize the Kv1.5 inhibitory activity of aryl sulfonamido tetralin **2a** (Fig. 1).[8]

A series of tetralins having substituent variations in the sulfonamido fragment was synthesized as shown in Scheme 1. Ketone reduction of 7-nitro-1-tetralone (**3**), dehydration, epoxidation with *m*-CPBA and ring opening with ammonium hydroxide gave the *trans*-amino alcohol **4**. Amine protection, nitro reduction and coupling with *m*-anisoyl chloride provided **5**. Deprotection followed by sulfonylation afforded analogs **2a**–**r**.

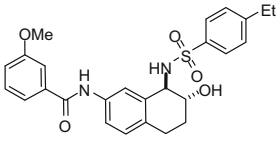
Aryl sulfonamido tetralins having substituent variations in amido fragment were prepared as described in Scheme 2. Certain amide bioisosteres were also synthesized. Sulfonylation of amino alcohol **4** with 4-ethylphenylsulfonyl chloride followed by nitro reduction provided aniline **6**. Coupling of **6** with carboxylic acids or acid chlorides gave the amido analogs **7a**–**n**.[9] The carbamate **7o** and urea **7p** were prepared by reacting **6** with benzyl chloroformate and benzyl isocyanate, respectively.

In order to determine if the 2-hydroxyl group interacted with the channel protein, aryl sulfonamido tetralins lacking this functionality were prepared (Scheme 3). Reductive amination of 7-nitro-1-indanone (**3**), sulfonylation and nitro reduction gave aniline **8**. Coupling of **8** with *m*-anisoyl chloride or hydrocinnamoyl chloride provided the des-hydroxy analogs **9a** and **9b**, respectively.

Aryl sulfonamido tetralins having more elaborate amido modifications were synthesized. These efforts were designed to incorporate an ionizable center into the molecule in an attempt to improve



1
Kv1.5 IC_{50} 0.16 μM



2a
Kv1.5 IC_{50} 0.44 μM

Figure 1. Structure of Kv1.5 inhibitors indane **1** and tetralin **2a**.

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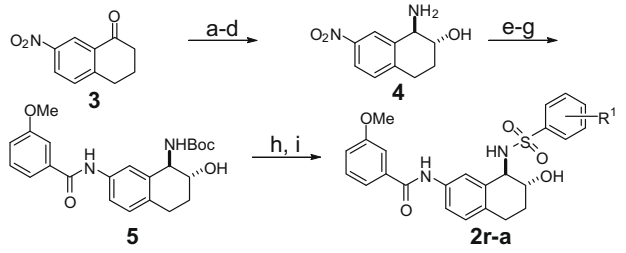
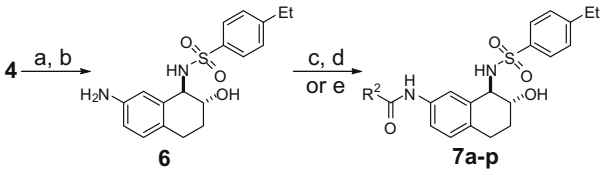
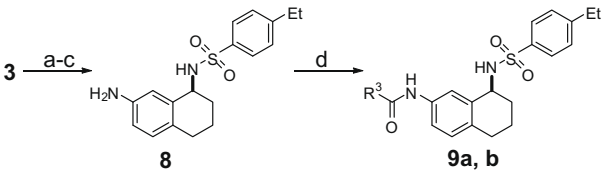


Scheme 1. Reagents and conditions: (a) $NaBH_4$, MeOH, 99%; (b) catalytic TsOH-H_2O, toluene, 100 °C, 100%; (c) *m*-CPBA, CH_2Cl_2, 100%; (d) NH_4OH, THF/EtOH, 50 °C, 89%; (e) Boc_2O, NEt_3, THF, 71%; (f) $NaBH_4$, catalytic $NiCl_2$, THF/MeOH, 89%; (g) *m*-anisoyl chloride, NEt_3, CH_2Cl_2, 81%; (h) 4 N HCl, dioxane, 86%; (i) R^1-$PhSO_2Cl$, catalytic DMAP, NEt_3, THF, 52% for **2d**.



Scheme 2. Reagents and conditions: (a) 4-Et-$PhSO_2Cl$, catalytic DMAP, NEt_3, THF, 67%; (b) $NaBH_4$, catalytic $NiCl_2$, THF/MeOH, 89%; (c) R^2COCl, NEt_3, DMF, 66% for **7l**; (d) R^2CO_2H, $(EtO)_2P(O)$–OBt, NEt_3 DMF, 18% for **7m**; (d) BnNCO, THF for **7p**, 48%.

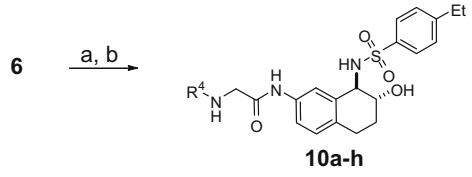


Scheme 3. Reagents and conditions: (a) NH_4OAc, $Na(CN)BH_3$, MeOH, 77%; (b) 4-Et-$PhSO_2Cl$, NEt_3, THF, 58%; (c) $NaBH_4$, catalytic $NiCl_2$, THF/MeOH, 97% (d) R^3COCl, NEt_3, THF, 78% for **9a**.

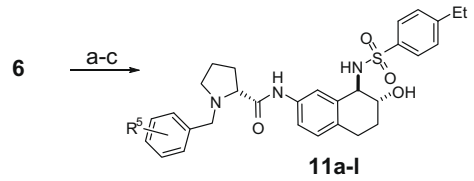
the aqueous solubility of these Kv1.5 inhibitors. Reaction of **6** with bromoacetyl bromide provided an α-bromoacetamido intermediate that participated in displacement reactions with aryl- or alkyl-amines to give glycinamido analogs **10a**–**h** (Scheme 4). Reaction of **6** with (*S*)-(−)-*N*-(trifluoroacetyl)prolyl chloride, deprotection and reaction with benzyl bromides gave the prolinamido analogs **11a**–**l** as a mixture of diastereomers (Scheme 5).

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.[10] Inhibition of the hERG current was also measured using EP. In this study, compounds were synthesized and tested as racemic mixtures.

We began this investigation by preparing aryl sulfonamido tetralins having substituent variations in the sulfonamide fragment as



Scheme 4. Reagents and conditions: (a) bromoacetyl bromide; NEt_3, DMF, 75%; (b) R^4NH_2, K_2CO_3, MeCN, 60% for **10a**.

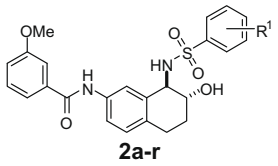


Scheme 5. Reagents and conditions: (a) (*S*)-(−)-*N*-(trifluoroacetyl)prolyl chloride, NEt_3, DMF, 59%; (b) K_2CO_3, H_2O, MeOH, 65%; (c) R^5-$PhCH_2Br$, K_2CO_3, MeCN, 70% for **11a**.

presented in Table 1. In order to rapidly establish a SAR, the amido fragment was held as *m*-anisoyl. Kv1.5 activity tended to improve as the size of the alkyl substituent in the 4-position increased from ethyl to *n*-pentyl (**2a**–**f**). Unfortunately, the improvement in potency achieved by adding more lipophilicity was offset by a corresponding reduction in aqueous solubility (see **2a** vs **2e**, Table 2). Replacing the ethyl of **2a** with a methoxy (**2j**) resulted in a considerable loss in activity. Methyl (**2h**), trifluoromethyl (**2i**), nitro (**2k**), halo (**2l**–**n**) and hydrogen (**2g**) substitution in the 4-position also resulted in compounds having diminished Kv1.5 activity relative to **2a**. Likewise, methyl (**2o**) or halo (**2p**–**r**) substitution in the 2- or 3-position was not tolerated.

Turning our attention to the amido portion of the molecule, the sulfonamide fragment was held as 4-ethylphenyl (Table 3). In the benzamido series, the 2- and 4-OMe analogs (**7b** and **7c**, respec-

Table 1
Kv1.5 activity of tetralins having sulfonamido variations



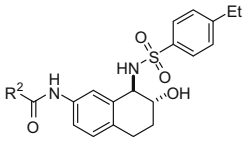
Compound	R^1	IC_{50} (μM) or inhibition at 1 μM[a]
2a	4-Et	0.44
2b	4-*n*-Pr	0.09
2c	4-*i*-Pr	0.43
2d	4-*n*-Bu	0.14
2e	4-*t*-Bu	0.16
2f	4-*n*-Pent	0.07
2g	H	14 ± 2%
2h	2-Me	30 ± 2%
2i	4-CF_3	21 ± 6%
2j	4-OMe	3.0
2k	4-NO_2	6 ± 2%
2l	4-Br	14 ± 12%
2m	4-Cl	11 ± 1%
2n	4-F	5 ± 1%
2o	3-Me	7 ± 1%
2p	3-Cl	2 ± 2%
2q	3-F	2 ± 2%
2r	2-F	3 ± 2%

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

Table 2
Aqueous solubility of Kv1.5 inhibitors[11]

Compound	μg/mL
2a	5
2e	0.3
7j	2
7l	0.6
9a	0.2
9b	<0.1

Table 3
Kv1.5 activity of tetralins having amido variations



7a-p

Compound	R^2	IC_{50} (μM) or inhibition at 1 μM[a]
7a	Ph	19 ± 4%
7b	2-OMe-Ph	0.45
7c	4-OMe-Ph	0.45
7d	2-Cl-Ph	28 ± 2%
7e	3-Cl-Ph	0.71
7f	4-Cl-Ph	0.34
7g	3,5-Di-OMe-Ph	0.64
7h	$PhCH_2$	22 ± 4%
7i	3-MeO-$PhCH_2$	28 ± 4%
7j	$PhCH_2CH_2$	0.25
7	$PhOCH_2$	22 ± 3%
7l	*trans*-PhCH=CH	0.20
7m	PhCC	0.43
7n	*trans*-Ph-cprop	0.35
7o	$PhCH_2O$	0.23
7p	$PhCH_2N(H)$	0.61

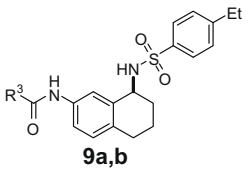
[a] Inhibition values are means of at least two experiments ± SEM.

tively) were about the same potency as the 3-OMe analog **2a**. A decrease in activity was observed with 3,5-di-OMe substitution (**7g**). Potency was improved slightly upon 4-Cl substitution (**7f**), but diminished with 2- and 3-Cl substitution (**7d** and **7e**, respectively). Albeit limited in scope, no firm SAR deductions could be made from this study. Other opportunities to increase Kv1.5 inhibitory activity with amido modifications were explored.

Phenacetamido analogs **7h** and **7i** were weak Kv1.5 inhibitors. Extending the methylene spacer to provide hydrocinnamamido derivative **7j** afforded a Kv1.5 inhibitor having improved potency relative to **2a**. Follow-up chemistry on this observation identified other compounds having good activity including the *trans*-cinnamamido **7l**, phenylpropynamido **7m** and *trans*-phenylcyclopropanamido **7n** analogs. A drop off in activity was observed with phenoxyacetamido **7k**. The benzyl carbamate **7o** and benzyl urea **7p** derivatives retain Kv1.5 potency indicating amido bioisosteres are tolerated. Once again, the aqueous solubility of at least two of these more lipophilic aryl sulfonamido tetralins (**7j** and **7l**) is diminished relative to **2a** (Table 2).

As we anticipated from previous studies with aryl sulfonamido indanes, the hydroxyl group on the tetralin scaffold was not a critical element of the Kv1.5 pharmacophore.[7] The des-hydroxy analogs **9a** and **9b** retained Kv1.5 inhibitory activity (Table 4). However, removing the hydroxyl group was problematic since the des-hydroxy analogs were at least 20-fold less soluble (see **2a** vs **9a**, and **7j** vs **9b**, Table 2).

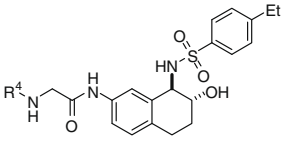
Table 4
Kv1.5 activity of des-hydroxy tetralins



9a,b

Compound	R^3	IC_{50} (μM)
9a	3-OMe-Ph	0.59
9b	$PhCH_2CH_2$	0.28

Table 5
Kv1.5 inhibition of glycinamido analogs



10a-h

Compound	R^4	1 μM[a] (%)
10a	Ph	10 ± 1
10b	2-Me-Ph	13 ± 1
10c	3-Me-Ph	25 ± 4
10d	3-OMe-Ph	39 ± 5
10e	4-Et-Ph	15 ± 2
10f	4-OMe	18 ± 3
10g	$PhCH_2$	31 ± 5
10h	$PhCH_2CH_2$	34 ± 3

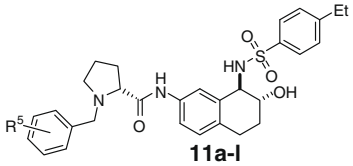
[a] Inhibition values are means of at least two experiments ± SEM.

Prompted by our desire to incorporate more polarity into these molecules in an attempt to improve the aqueous solubility, we prepared a series of glycinamido analogs (**10a**–**h**). Compound **10a** was a weak Kv1.5 inhibitor. As presented in Table 5, neither substitution on the phenyl ring (**10b**–**f**) nor chain extension to give the benzyl **10g** or phenethyl **10h** derivatives significantly improved activity.

We continued to search for opportunities to incorporate a basic center into the amido side chain and discovered that the diastereomeric prolinamido analogs **11a**–**l** were potent Kv1.5 blockers. A variety of phenyl substitution patterns were equally well tolerated (Table 6). It is noteworthy that **11a** is considerably more active than the isosteric glycinamido analog **10g**. The conformational constraint imposed by the pyrrolidine ring may be responsible for the increase in potency.

Selected compounds were tested for their ability to inhibit the hERG potassium channel. These data are presented in Table 7. Inhibition of this cardiac current is problematic due to the potential induction of unwanted ventricular side effects.[12] We were satisfied with the selectivity of **2b** that we estimated to be >100-fold (Kv1.5 IC_{50} 0.09 μM; hERG <50% inhibition at 10 μM). Unfortunately, prolinamido analogs **11c** and **11f** did not display this level of selectivity and our interest in this chemical series was diminished.

Table 6
Kv1.5 activity of prolinamido analogs



11a-l

Compound	R^5	IC_{50} (μM) or inhibition at 1 μM[a]
11a	H	77 ± 2%
11b	2-Cl	87 ±2%
11c	3-Cl	0.22
11d	3-CF_3	89 ± 3%
11e	3-OCF_3	0.29
11f	3-OMe	0.30
11g	3-Me	78 ± 2%
11h	4-Cl	92 ± 1%
11i	4-CF_3	89 ± 1%
11j	4-OCF_3	86 ± 1%
11	4-Me	75 ± 1%
11l	4-*t*-Bu	80 ± 6%

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

Table 7
hERG inhibiton of tetralins

Compd	10 μM[a] (%)
2b	39 ± 2
11c	77 ± 5
11f	50 ± 6

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

In summary, we have discovered that aryl sulfonamido tetralins are Kv1.5 inhibitors. Investigation of the sulfonamido fragment revealed a tight SAR with strong preference for *para*-alkyl substitution on the phenyl ring. In contrast, a more diverse set of variations was tolerated on the amido portion of the molecule. hERG selectivity became a concern when a basic nitrogen was introduced. In subsequent publications we will discuss our efforts to design aryl sulfonamido tetralin Kv1.5 inhibitors having improved potency and selectivity coupled with more desirable physiochemical properties.

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