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Evolution of thiazolidine-based blockers of human Kv1.5 for the treatment of atrial arrhythmias

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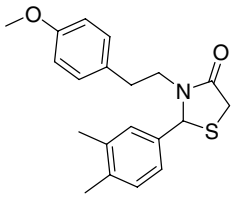
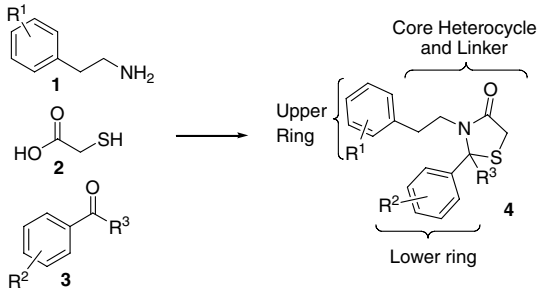
Abstract—Blockade of the Kv1.5 ion channel is a potentially atrial-selective avenue for the treatment of atrial fibrillation and atrial flutter. The development and biological evaluation of a series of thiazolidine-based blockers of Kv1.5 is described.

Atrial flutter and atrial fibrillation are the most common cardiac arrhythmias and they are associated with an increase in heart failure, stroke, and mortality.[1–3] Atrial fibrillation affects three million Americans and leads to 80,000 strokes each year. Irregular propagation of the cardiac impulse leads to fibrillation. One approach to prevent fibrillation involves increasing myocardial refractoriness by blockade of repolarizing currents carried by potassium ion (K^+) channels. Most currently marketed antiarrhythmic agents block the hERG channel and the associated I_{Kr} repolarizing current which is present in both the atria and the ventricles. While blockade of hERG in the atria can reduce atrial arrhythmias, blockade of hERG in the ventricles leads to a prolongation of the QT interval and an increased propensity for life-threatening ventricular arrhythmias. Blockade of atrial-selective K^+ channels could provide an approach for control of atrial arrhythmias that is devoid of adverse ventricular effects. One such atrial-selective channel is Kv1.5 which carries the ultrarapid delayed rectifier current I_{Kur}.[4–6] The I_{Kur} current functions selectively in human atrial cells so blockade of Kv1.5 may provide a promising approach for the development of safe and effective drugs for prevention of atrial arrhythmias.[7,8] Several companies have pursued Kv1.5 inhibitors and much of this work has been summarized in recent reviews.[9,10]



I

We began our search for novel Kv1.5 blockers with the vicinally-substituted thiazolidinone class first reported by Icagen.[11] Our goal was to determine the scope of vicinally-substituted heterocycles as Kv1.5 blockers starting from the thiazolidinone class as a prototype. Thiazolidinones **4** were synthesized (Scheme 1) in a 3-



Scheme 1. Conditions: THF reflux.

Keywords: Atrial fibrillation; Potassium channel; Human Kv1.5; Thiazolidine; Atrial-selective.
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component 1-pot reaction, with mercaptoacetic acid, a phenethylamine, and an arylaldehyde. We chose to begin our work by exploring the Kv1.5 blocking ability of compounds with two key structural changes: (1) ketone rather than aldehyde-derived thiazolidinones and (2) incorporation of the carbonyl group in the linker rather than the heterocyclic ring in the form of acylthiazolidines.

At the outset, several benchmark thiazolidinones were prepared and we soon discovered that a methoxy group was preferred in the upper ring and that both electron donating and electron withdrawing groups were allowed in the lower ring (Table 1). Compound **I**, with a *p*-methoxy in the upper ring and a 3,4-dimethyl arrangement in the lower ring, was a potent Kv1.5 blocker with an IC_{50} value of 137 nM, in good agreement with the value reported by Icagen.

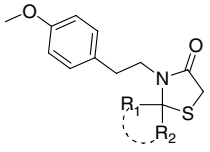
The ketone-derived thiazolidinones **4a–d** were prepared from a series of substituted indanones and acetophenones. The data in Table 1 show that compounds in both series are sub-micromolar blockers of Kv1.5. The most potent compound, **4d**, derived from 3,4-dimethylacetophenone has an IC_{50} value of 69 nM, about twice the potency of the Icagen compound **I**.

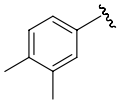
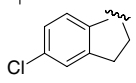
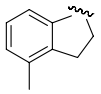
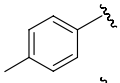
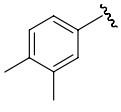
Both the Icagen compound and the ketone-derived thiazolidinones had low aqueous solubility ranging from ~5 to 50 μg/mL. As an approach to improve solubility, we replaced one of the carbons in the linker with oxygen to provide *N*-alkoxythiazolidinones. The *N*-hydroxy intermediate **5** was prepared using the same synthetic methodology used for the thiazolidinones but employing hydroxylamine in place of the phenylalkylamine. Alkylation with substituted or unsubstituted benzyl bromides using DBU as a base provided the target blockers **6** (Scheme 2).

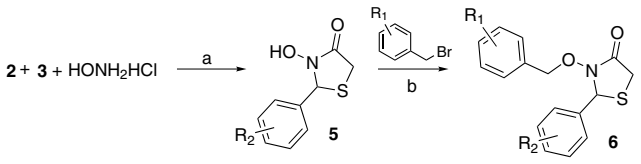
We began this investigation with an unsubstituted phenyl for the upper ring. From our previous work, we observed that three lower ring substitutions consistently provided active blockers; namely 4-Cl, 3,4-di-Cl, and 3,4-di-CH_3. As expected, compounds **6a–c** (Table 2) were effective blockers of Kv1.5 with the 3,4-dimethyl compound **6c** being the most potent. Next, we prepared four compounds with a *p*-methoxy R1 group in the upper ring (**6d–g**). Compound **6d**, where there is no substitution on the lower aryl ring (R_2 = H), gave an IC_{50} more than five times greater than the others in this set. The remaining three compounds (**6e–g**) were about two- to fivefold more potent than the corresponding des-methoxy compounds (**6a–c**), reinforcing the observation that a methoxy in the upper ring increases potency. Next, the effect of varying the position of the methoxy group on the upper ring was examined. The 3-methoxy compounds (**6h–i**) and the 2-methoxy compounds (**6k–m**) had similar potencies and each of these compounds was about twofold less potent than the corresponding 4-methoxy analog.

We next turned to changes in the thiazolidinone scaffold to determine if the intact thiazolidinone was an essential part of the pharmacophore or if it might serve primarily as a scaffold for display of the upper and lower rings. Thus, we moved the carbonyl group outside of the ring, giving rise to thiazolidine amides and carbamates. The chemistry (Scheme 3) began with reaction of an aldehyde **3** and cysteamine hydrochloride **7** to provide the 2-arylthiazolidine **8** which was then acylated with an

Table 1. Blockade of Kv1.5 by ketone-derived thiazolidinones



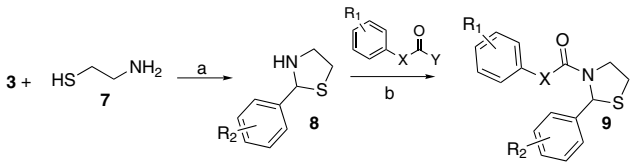
Compound	R_1	R_2	% Block at 1 μM	Kv 1.5 IC_{50} (μM)
I		H		0.137
4a			66	0.812
4b			61	0.487
4c		CH_3	88	0.390
4d		CH_3	96	0.069



Scheme 2. Conditions: (a) THF reflux and (b) DBU, DMF.

Table 2. Blockade of Kv1.5 by *N*-alkoxythiazolidinones

Compound	R_1	R_2	%Block at 1 μm	Kv 1.5 IC_{50} (μM)
6a	H	4-Cl	35	0.997
6b	H	3, 4-di-Cl	77	0.463
6c	H	3, 4-di-CH_3	92	0.207
6d	4-OMe	H	NT	0.924
6e	4-OMe	4-Cl	NT	0.187
6f	4-OMe	3, 4-di-Cl	92	0.113
6g	4-OMe	3, 4-di-CH_3	NT	0.095
6h	3-OMe	4-Cl	NT	0.380
6i	3-OMe	3, 4-di-Cl	NT	0.179
6j	3-OMe	3, 4-di-CH_3	75	0.269
6k	2-OMe	4-Cl	25	NT
6l	2-OMe	3, 4-di-Cl	NT	0.204
6m	2-OMe	3, 4-di-CH_3	92	0.177



Scheme 3. Conditions: (a) TEA, DMF and (b) TEA, CH_2Cl_2.

Table 3. Blockade of Kv1.5 by thiazolidine carbamates (R_1 = H, X=CH_2O)

Compound	R_2	%Block at 1 μm	Kv1.5 IC_{50} (μM)
9a	4-Me	80	
9b	4-OMe	72	
9c	4-c-Pr	64	
9d	4-N(Me)$_2$	55	
9e	3, 4-di-CH_3	95	0.162
9f	3, 4-di-Cl	93	
9g	4-OMe, 3-Cl	35	

appropriate acid, acid chloride or chloroformate, giving the target compounds **9**.

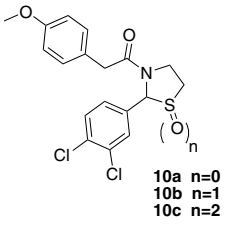
A series of compounds (**9a**–**g**) was made using benzyl chloroformate for the acylating agent (R_1 = H) and seven different substitutions (R_2) in the lower ring (Table 3). These were screened at 1 μM concentration for block of Kv1.5. All the compounds except for **9g** produced at least 50% inhibition of current. The 3,4-d-CH_3 and 3,4-di-Cl, compounds **9e** and**9f**, were the most active, with the 3,4-di-CH_3 compound **9e** giving an IC_{50} similar to the corresponding *N*-alkoxythiazolidinone **6c** (Table 2). These results demonstrate that the carbonyl group does not need to be part of the heterocyclic ring and provided the first data to suggest that the heterocyclic ring might serve primarily as a scaffold for appropriate orientation of the vicinal side chains.

We then changed our focus to amides (Table 4) **9h**–**m**. The first amide that we made, **9h**, reversed the CH_2O orientation in the linker versus the corresponding carbamate **9e** which resulted in a dramatic loss in activity. Next, we examined a series of homologous compounds with all carbon linkers **9i**–**m**. All the compounds showed good blockade with the two carbon linker, compound **9k**, the most active in the saturated series. IC_{50} determinations confirmed that the two carbon linker provided a more potent compound than the one carbon linker (**9k** vs **9j**). Adding rigidity to the two carbon linker in the form of an alkene provides compound (**9l**) that retained good activity.

Although these compounds had good activity in cell-based assays, they were rapidly metabolized. When compound **10a** was incubated with rat S9 microsomal fraction for 30 min, no parent compound remained. Our hypothesis was that either oxidation of the ring sulfur or demethylation of the *p*-methoxy in the upper ring would be the most likely sites were the most likely metabolic events. We synthesized the proposed sulfoxide and sulfone metabolites **10b** and **10c**, and they were compared by LCMS with the isolate from the S9 assay.

Table 4. Blockade of Kv1.5 by thiazolidine amides (R_2 = 3,4-di-Me)

Compound	X	R_1	% Block at 1 μm	Kv1.5 IC_{50} (μM)
9h	OCH_2	H	18	
9i	CH_2CH_2	H	87	
9j	CH_2	OMe	77	0.537
9k	CH_2CH_2	OMe	89	0.150
9l	CH=CH	OMe	92	
9m	$CH_2CH_2CH_2$	OMe	68	



The result confirmed that the sulfur was the main site for metabolic oxidation. This prompted us to abandon the thiazolidinone scaffold and to explore isosteric alternatives that might provide more metabolically stable compounds. These efforts will be reported separately.

Acknowledgments

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