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Discovery of triarylethanolamine inhibitors of the Kv1.5 potassium channel

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ABSTRACT

A series of triarylethanolamine inhibitors of the Kv1.5 potassium channel have been prepared and evaluated for their effects in vitro and in vivo. The structure–activity relationship (SAR) studies described herein led to the development of potent, selective and orally active inhibitors of Kv1.5.

The most common sustained cardiac arrhythmia is atrial fibrillation (AF), which afflicts ~1% of the overall US population with higher prevalence in the elderly population and occurs more often in men than women.[1–4] The associated morbidity, mortality, quality of life and notably increased risk of stroke associated with AF patients present a significant unmet medical need.[2] Current antiarrhythmic therapies inhibit multiple ion channels present in both the ventricle and atrium and have significant limitations and adverse effects, most significantly the potential for ventricular proarrhythmia, which has led to the pursuit of atrial selective therapies that offer potentially safer treatment options for patients suffering from AF.[5,6]

The ultra-rapid delayed rectifier current I_{Kur}, which is expressed in human atrium and not the ventricle, has emerged as a promising target for atrial selective therapy. The voltage gated Kv1.5 ion channel underlies the native cardiac I_{Kur} current that is involved in the repolarization of atrial action potential.[7,8] Additionally, inhibition of I_{Kur} has been shown to increase atrial refractory period and restore normal sinus rhythm during arrhythmia, a critical objective to the development of new, more effective and safer treatments for AF, as recurrent arrhythmia leads to persistent AF and atrial remodelling, a condition that is resistant to existing drug therapies.[5] As such, the development of selective inhibitors of Kv1.5 offer a promising strategy for the termination and/or prevention of AF.[9] Indeed, several research groups have disclosed Kv1.5 blockers that have shown promise for the development of novel atrial selective antiarrhythmic agents.[10] Herein, we describe the discovery of orally bioavailable, potent and selective triarylethanolamine inhibitors of the Kv1.5 potassium channel.[11]

Investigations at Merck led to the identification of diphenyl phosphine oxide (DPO)[12] inhibitors (**1**, Fig. 1), which have been well characterized both in vitro and in vivo for their inhibitory activity against Kv1.5.[13,14] While studies of isoquinoline blockers (i.e., ISQ-1) were ongoing,[15] a structurally diverse series was sought. Compound **1** is highly lipophilic (*c*Log *P* = 5.67) and an improved lead was desired that possessed properties suitable for oral dosing. Employing 2-D scaffold hopping, similarity searches and screening approaches led to the identification of triarylethanolamine **2**, which is potent blocker of Kv1.5 (IC_{50} = 204 nM). While **2** possesses improved properties relative to **1** (i.e., increased PSA and reduced *c*Log *P*), further optimization of physiochemical prop-

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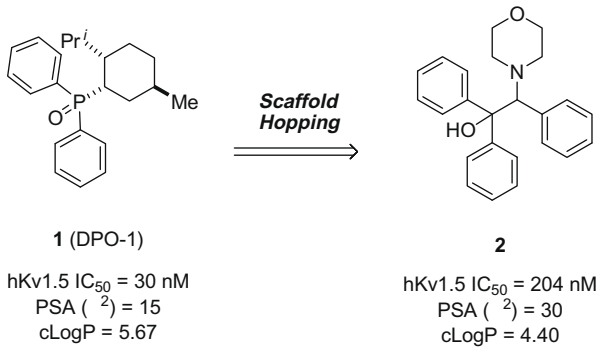
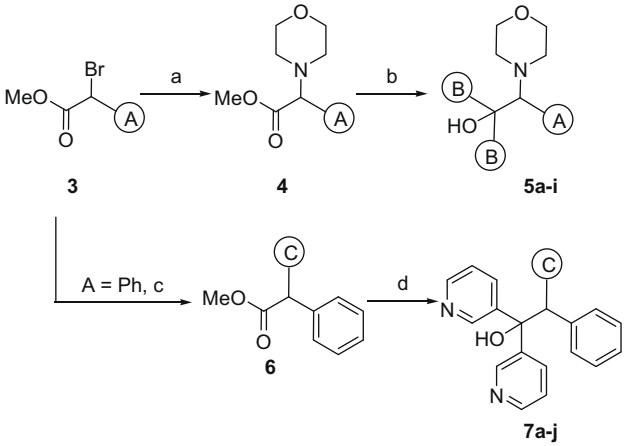


Figure 1. DPO-1 (**1**) and triaryethanolamine (**2**) Kv1.5 blockers.

erties were required to obtain a compound suitable for in vivo characterization.

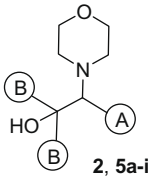
Compounds were prepared according to the general procedures described in Scheme 1, in which complimentary routes were utilized to survey variations of the aryl and amino groups. Alkylation of substituted α-bromo esters **3** with morpholine afforded amines **4**, which were treated with organolithium reagents to afford morpholinoethanols **5a**–**i**. An additional subset of compounds were prepared employing methyl α-bromo(phenyl) acetate via S_N2 displacement with various amines to afford **6**, which upon subsequent treatment with 3-pyridyl lithium afforded compounds **7a**–**j**.[16]

Compound potency was determined in a high-throughput patch clamp (HT-clamp) assay in which CHO cells expressing the human Kv1.5 channel were employed.[17] Selectivity over the human ether-a-go-go-related channel (hERG), which underlies the native cardiac potassium current I_{Kr}, present in both human atrium and ventricle, was of primary concern for an atrial selective therapy and was monitored due to the known proarrhythmic potential of I_{Kr} blockers.[18] Table 1 depicts SAR related to the triphenyl moiety of **2**. These studies revealed that both geminal aromatic B-rings were required (**5a**–**b** vs **2**) for Kv1.5 activity. The phenyl B-ring was readily substituted with 3-pyridyl moieties to afford **5d** without a significant loss in potency. Replacement of the phenyl A-ring (**5c**, **e**–**i**) was met with some success, although longer aliphatic groups only offered moderately potent blockers. Also, replacement of a phenyl with a benzyl group (**5g**) was a poorly tolerated, resulting in a 20-fold loss in potency. Relative to **2**, compound **5d** was equipotent,



Scheme 1. General preparation of Kv1.5 blockers. Reagents and conditions: (a) morpholine, triethylamine, acetonitrile; (b) organolithium, tetrahydrofuran, −78 to 0 °C; (c) amine, triethylamine, acetonitrile; (d) 3-pyridyl lithium, tetrahydrofuran, −78 to 0 °C.

Table 1
In vitro inhibitory activity of triarylethanolamines



2, **5a-i**

Compound	A	B	Kv1.5 IC$_{50}$[a,b] (nM)	hERG IC$_{50}$[c] (nM)
5a	Ph	H	>60,000	>60,000
5b	Ph	Me	>60,000	>60,000
2	Ph	Ph	204	>65,000
5c	iPr	Ph	3242	>30,000
5d	Ph	3-Pyridyl	256	>60,000
5e	Me	3-Pyridyl	>60,000	>60,000
5f	iPr	3-Pyridyl	2140	75,000
5g	Bn	3-Pyridyl	4946	15,190
5h	nBu	3-Pyridyl	2869	36,000
5i	nHex	3-Pyridyl	3357	27,500

[a] Determined according to Ref. 17. Potency values (IC$_{50}$s) were determined using a high-throughput patch clamp assay with 10-point dose response curves, n = 3–4 cells per point.
[b] ISQ-1 was used as a positive control, see Ref. 15.

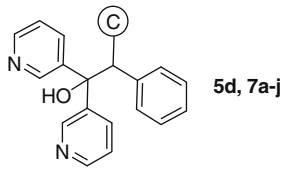
exhibited higher PSA and had a decreased *c*Log *P*, which we postulated would improve physiochemical properties (vide infra).

Optimization of the amino group was explored in the context of the improved bispyridyl scaffold (Table 2). Removal of the morpholino moiety (i.e., **7a**), as well as replacement with an unsubstituted amino group (i.e., **7b**), proved to decrease Kv1.5 blockade. However, the introduction of small aliphatic substituents on the amino group restored Kv1.5 potency (**7c**–**e**). Introduction of the 1,4-oxazepane (**7g**) or the ring-opened analogue *N*-methyl-2-(methyloxy)ethanamine (**7f**) was well-tolerated, but selectivity over hERG was diminished (~7-fold) for both compounds. Furthermore, the introduction of a piperazine (**7h**) completely eroded selectivity versus hERG. Fortuitously, removal of the basic nitrogen from **7h** afforded piperidine **7i**, which exhibited good Kv1.5 potency and restored hERG selectivity. Incorporation of a pyrrolidine was also well-tolerated, affording the even more selective blocker versus hERG **7j**.

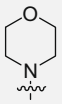
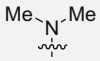
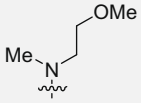
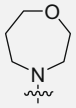
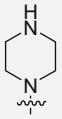
With several potent Kv1.5 blockers identified and mindful that the initial lead compound **2** exhibited a poor solubility profile, an assessment of physiochemical properties suitable for oral dosing was conducted. Table 3 depicts solubility data of selected Kv1.5 blockers **5d**, **7i** and **7j**. Unlike the poorly soluble lead compound **2**, compound **5d** exhibited moderate solubility in aqueous buffered solution. Substitution of the morpholine for the piperidine **7i** led to a 10-fold decrease in aqueous solubility. Interestingly, the pyrrolidine blocker **7j** exhibited a threefold increase in solubility at pH 7.4, relative to **5d**, and decreasing the pH further to 5.2 led to enhanced aqueous solubility of greater than 1 mg/mL, presumably as a result of protonation of the basic pyrrolidine. Due to the enhanced physiochemical properties, in addition to the low protein binding of **7j** relative to **7e** (25% bound vs 82%, respectively), **7j** was selected for further evaluation.

Rat pharmacokinetic studies were carried out on triarylethanolamine (TAEA) **7j**, which exhibited high clearance (59 mL/min/kg) but a high volume of distribution (3.4 L/kg), leading to a half life of 1.1 h. Relative to the initial lead **2**, **7j** possesses increased polar surface area (46 Å^2), good solubility and reduced *c*Log *P* (2.44), making it an attractive candidate for in vivo profiling. Electrophysiological (EP) studies were carried out on surgically instrumented, anesthetized rats,[20] which were infused intravenously with **7j** (Fig. 2). Various cardiac parameters were recorded, including atrial

Table 2
In vitro inhibitory activity of triarylethanolamines



5d, 7a-j

Compound	C	Kv1.5 IC_{50}[a,b] (nM)	hERG IC_{50}[c] (nM)
5d		256	>60,000
7a	H	7107	>60,000
7b[d]	NH_2	16,390	>60,000
7c		850	>60,000
7d		2222	15,000
7e		234	>60,000
7f		583	3450
7g		517	3550
7h		7935	2300
7i		206	14,000
7j		284	20,000

[a] Determined according to Ref. 17. Potency values (IC_{50}s) were determined in a high-throughput patch clamp assay from 10-point dose response curves, $n = 3$–4 cells per point.
[b] ISQ-1 was used as a positive control, see Ref. 15.
[c] See Ref. 19.

Table 3
Aqueous solubility of selected triarylethanolamines

Compound	Solubility[a]	pH[b]
5d	0.043	7.2
7i	0.0054	7.4
7j	0.11	7.4
7j	1.4	5.2

[a] Solubility is expressed in mg/mL in aqueous buffer at listed pH. All compounds tested were crystalline by microscopic examination under plain polarized light; however the specific crystalline form was not determined.
[b] pH of buffered aqueous solution.

refractory period (ARP) and ventricular refractory period (VRP). Because I_{Kur} is functionally expressed in both the atria and ventricular cardiac tissues of rats, this model is restricted only to the assessment of efficacy and cannot address atrial selectivity. Compound **7j** exhibited a dose-dependent increase in both ARP and VRP. Importantly, these robust effects on cardiac repolarization occurred without significantly affecting atrio-ventricular conduction, as there were no changes observed in AV nodal refractoriness (AVRP). At the highest dose tested, **7j** exhibited a 79% increase in ARP and a 63% increase in VRP at plasma levels of <10 μM. These results are superior to those previously reported for rat EP experiments that evaluated isoquinoline-derived Kv1.5 blockers (see Ref. 15). The superiority of **7j** is reflected in the magnitude of percent change in ARP and VRP achieved at ~3-fold lower plasma concentrations, which is likely due the large free fraction of **7j** (hFF = 25%). In a canine heart failure model, **7j** also terminated pacing-induced AF and induced significant prolongation of ARP but notably had no effect on VRP at the highest dose tested, substantiating the atrial selectivity associated with inhibition of the Kv1.5 channel.[21] Thus, these findings are consistent with the profile of an I_{Kur} selective compound.

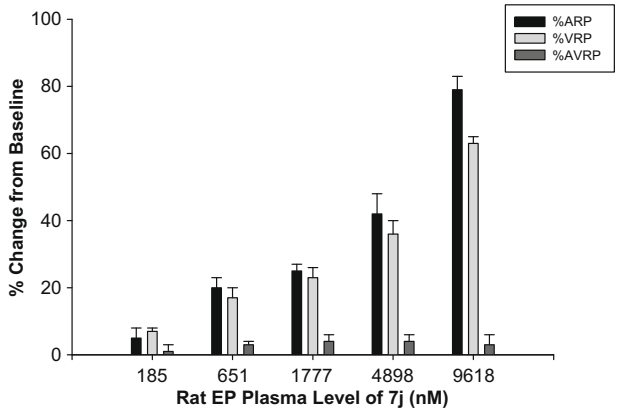


Figure 2. Rat EP profile of TAEA **7j** following 20 min infusions at 0.01, 0.03, 0.06, 0.2 and 0.6 mpk/min.

During the evaluation of **7j** in additional rodent and canine models, dose-dependent transient adverse effects (AEs) were observed at exposures similar to those eliciting EP effects in the aforementioned rat model, including shaking, tremors, twitching and convulsions. Studies were carried out to determine if these AEs were derived from neurological activity of the compound. In vitro experiments revealed that compound **7j** possesses good passive cell permeability and is not a rat P-gp substrate (Table 4). Brain penetration of **7j** was also evaluated in rats after a 1 h intravenous infusion in tail vein and showed that **7j** exhibits good brain penetration with a brain/plasma (B/P) ratio of 0.58. In addition, rat EEG studies were carried out, revealing abnormally high frequency contributions from 40 to 50 Hz upon administration of **7j** (data not shown), suggesting a pharmacological CNS effect on Kv1.x channels due to presence of the compound in brain.

The brain penetration and EEG studies performed suggest that the AEs observed with **7j** are neurologically related. Furthermore, voltage gated potassium channels are known to be expressed in the CNS and both channel openers and blockers have been targeted

Table 4
Brain penetration, passive permeability and P-gp efflux of compound **7j**

Compound	[Plasma][a,b] (μM)	[Brain][a,b] (μM)	B/P ratio[c]	% FF	Papp[d]	rP-gp[e]
7j	23.4	13.7	0.58	25	36	1.2

[a] Brain and plasma levels were determined following a 1 h tail vein iv infusion, 435 μg/min kg.
[b] $n = 3$ and is expressed as an average.
[c] B/P = [Brain]/[Plasma] expressed as a ratio.
[d] Passive permeability is expressed as 10^{-6} cm/s.
[e] Rat P-gp efflux values were determined in CHO cell lines over expressing rat P-gp (mdr1a). Values shown are a ratio of (B to A)/(A to B).

as potential therapeutic agents for CNS diseases.[22–24] Therefore, the development of a peripherally restricted Kv1.5 antagonist, which minimizes the potential for central nervous system exposure and inhibition of potassium channels in brain, is anticipated to afford an improved safety profile. Efforts aimed at addressing this hypothesis have been pursued[25] and will be the subject of future publications.

In conclusion, similarity searching of DPO inhibitors led to the identification of a class of triarylethanolamine Kv1.5 antagonists. Poor physical properties of the initial lead were overcome by replacement of the bisphenyl alcohol with a bispyridyl alcohol moiety and these studies led to the identification of TAEA **7j**, a potent inhibitor of Kv1.5 channels with desirable physical properties. TAEA **7j** exhibited robust electrophysiological effects on atrial repolarization but not atrioventricular conduction (AVRP) in vivo in rats and was found to be atrial selective in dogs. During the course of in vivo studies, neurological side effects were observed with TAEA **7j**. Subsequent studies suggested that the optimization of a peripherally restricted and selective Kv1.5 blocker that possesses good physical properties, robust electrophysiological effects and reduced central penetration may provide an efficacious agent with an acceptable safety profile.

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