

New Drugs Targeting the Cardiac Ultra-Rapid Delayed-Rectifier Current (I_{Kur}): Rationale, Pharmacology and Evidence for Potential Therapeutic Value

John W. Ford, PhD and James T. Milnes, PhD

Abstract: There is a clear unmet medical need for new pharmacologic therapies for the treatment of atrial fibrillation (AF) with improved efficacy and safety. This article reviews the development of new and novel Kv1.5/ultra-rapid delayed-rectifier current (I_{Kur}) inhibitors and presents evidence that Kv1.5 modulation provides an atrial-selective mechanism for treating AF. Academia and industry have invested heavily in Kv1.5 (>500 scientific publications and >50 patents published since 1993); however, to realize the full value of this therapeutic drug target, clinical efficacy and safety data are required for a selective Kv1.5 modulator. The reward for demonstrating clinical efficacy and safety in a pivotal Phase 3 trial, on regulatory approval, is “first in class” status.

Key Words: atrial fibrillation, atrial flutter, I_{Kur} , Kv1.5, ultra-rapid delayed rectifier, cardiac, heart, arrhythmia

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INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia facing physicians, afflicting 13% of men and 11% of women older than 85 years of age.^{1,2} With recent epidemiologic studies estimating that there are more than 11 million people with AF in the 7 major economies^{2–5} at an estimated cost of \$3600 per patient per year,⁶ the global economic burden of AF is significant. Increased life expectancy (eg, improved treatments for cardiovascular disease and stroke), the development of cardiac monitoring techniques capable of detecting paroxysmal (infrequent self-terminating) AF and asymptomatic AF, and a change in the definition of AF that now includes secondary AF have contributed to an increase in the prevalence of AF.⁵ The prevalence of AF is predicted to increase 2- to 3-fold in the United States from 2005 to 2050 and cause a further increase in the associated financial burden.³

AF is clinically significant because it contributes to the incidence of heart failure and stroke and also to overall

cardiovascular morbidity and mortality. Data from the Framingham Heart Study show that AF is associated with a 1.5- to 1.9-fold higher risk of death, much of which results from thromboembolic stroke.⁷ Patients with AF have a 5-fold increased risk for stroke; indeed, in the United States approximately 15% to 25% of all strokes can be attributed to AF.⁸ This figure will increase if the ongoing ASSERT (ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and the atrial fibrillation Reduction atrial pacing Trial) study confirms a relationship between asymptomatic AF and stroke.⁹ In addition to stroke, AF is implicated in hemodynamic dysfunction, tachycardia-induced cardiomyopathy, and systemic embolism, and all have a substantial impact on quality of life.

The etiology of AF is complex; AF can be triggered by ectopic activity, single-circuit reentry, or multiple circuit reentry.¹⁰ Current strategies for the control of AF involve either sinus rhythm (SR) maintenance or heart rate control. Although there is a consensus among cardiologists that SR control is the preferred and most effective treatment of AF, none of the SR control drugs currently available are able to maintain rhythm without significant negative side effects.^{11,12} For example, the available agent that is most effective, amiodarone, causes serious adverse effects including pulmonary toxicity (1%–17%), corneal microdeposits (>90%), optic neuropathy/neuritis (1%–2%), blue–grey skin discoloration (4%–9%), photosensitivity (25%–75%), hypothyroidism (6%), hyperthyroidism (0.9%–2%), peripheral neuropathy (0.3%), and hepatotoxicity (15%–30%).¹³ Class Ia antiarrhythmics (eg, quinidine) are associated with torsade de pointes (TdP)¹⁴; Class Ic antiarrhythmics (eg, flecainide) increase mortality in patients with ischemic and structural heart disease¹⁴; and all of the currently used Class III antiarrhythmic agents lack atrial specificity and therefore may possess a highly undesirable proarrhythmic liability in the ventricles, which can lead to TdP and sudden cardiac death.¹⁵ Thus, there is a clear unmet medical need for new pharmacologic AF therapy with improved efficacy and safety.¹

To address this unmet medical need, the pharmaceutical industry is searching for novel atrial-selective antiarrhythmic agents with a much improved efficacy and safety profile.¹⁶ An emerging putative atrial-selective drug target is Kv1.5, which has been shown to underlie the cardiac ultra-rapid delayed-rectifier (I_{Kur}) current in humans^{17–19} and, importantly, displays atrial-specific expression in the heart.^{20–22} Therefore, selective Kv1.5 blockers are thought to represent a safer pharmacologic

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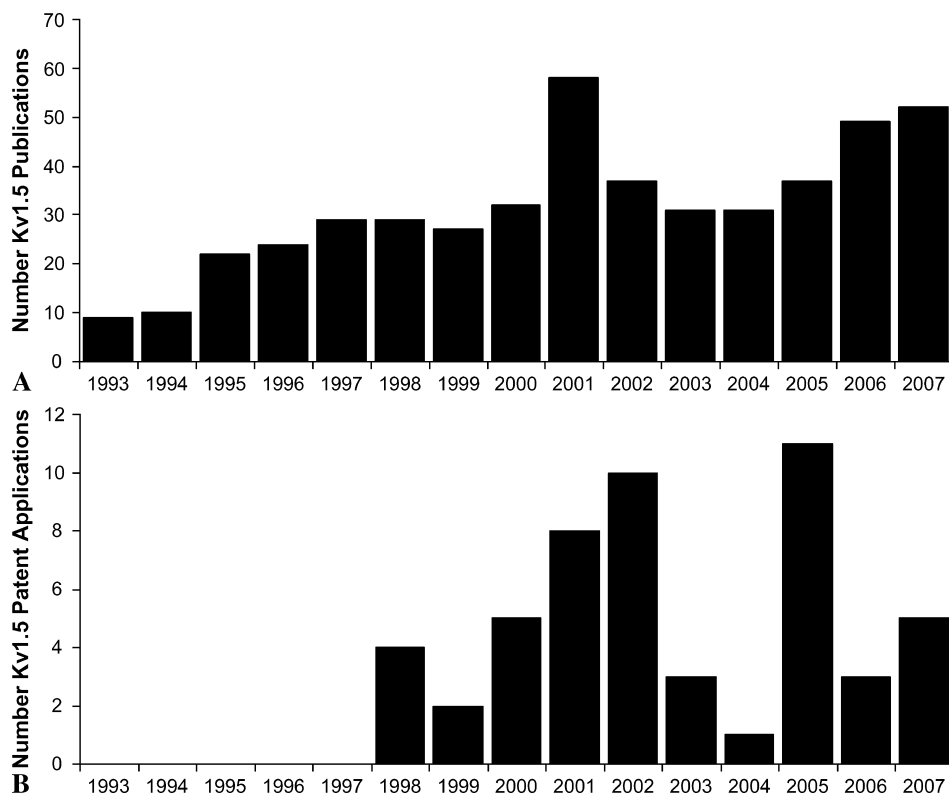


FIGURE 1. The number of published papers/patents relating to Kv1.5 per year. Panel A shows the number of Kv1.5 publications cited in PubMed between 1993 and 2007. Panel B shows the number of Kv1.5 inhibitor chemistry patents cited in the PCT and Aureus patent databases.

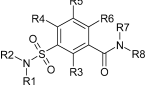
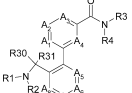
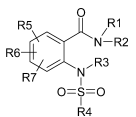
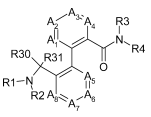
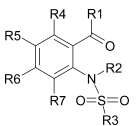
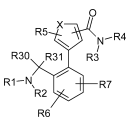
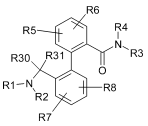
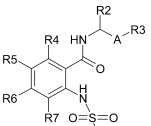
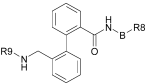
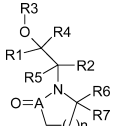
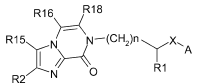
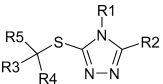
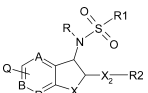
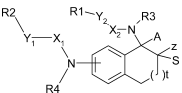
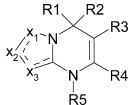
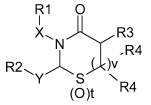
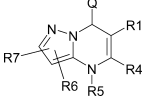
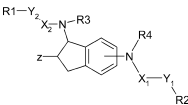
intervention strategy for pharmacologic cardioversion of AF and the prevention of recurrence of AF when compared with existing Class III antiarrhythmics. In addition to antiarrhythmic activity, Kv1.5 blockers may also improve atrial contractility and reduce thromboembolic risk.^{23,24}

Kv1.5 has been the focus of intense research by academia and industry alike, with >500 scientific publications and >50 patents published since 1993; See Figure 1. This article reviews the development of new and novel small molecule Kv1.5 inhibitors by a number of companies over the last decade. Compounds are grouped according to company and chemical class, and evidence for their potential value for treating AF is discussed. New compounds that preferentially block Kv1.5 at therapeutically relevant doses are included in this review. To focus this review, compounds for which only Kv1.5 current inhibition data exist are not covered in detail (Table 1). Peer-reviewed publications (full papers and scientific abstracts), patents, and company information (press releases, annual reports, Web sites) provided the content for this review. It should be noted that the claims of patents and company literature are not subject to the rigors of expert peer review.

Animal models are essential tools in the investigation and development of drug therapies for AF and atrial flutter (AFL). A number of species and models have been used. It is important that the model represents the human condition to as great an extent as is possible or is at least predictive of efficacy in man. A number of species have been used to investigate the efficacy of $I_{K_{ur}}$ blockers in the prevention or termination of AF. Similar to man^{17–19,25} Kv1.5 is the molecular correlate of $I_{K_{ur}}$ in the dog,^{26–29} pig,³⁰ and

rat^{27,31} and plays an important functional role in repolarization in the atria. In other species the molecular physiology of repolarization of the atria is less well understood. Studies have shown Kv1.5 ribonucleic acid is highly expressed in the rabbit,³² goat,³³ and African green monkey³⁴ atria, and protein expression has been reported in the atria and sinoatrial node of ferret and guinea pig atria.³⁵ However, electrophysiologic data to support a functional role of Kv1.5/ $I_{K_{ur}}$ in repolarization of these species are lacking. The most commonly used large species are dog, goat, and pig. Kv1.5 messenger ribonucleic acid (mRNA) and protein have been detected in canine atrial and ventricular tissue and are reported to be the molecular correlate of $I_{K_{ur}}$ in dog atrial²⁶ and ventricular³⁶ myocytes. Thus, although dog is a relevant species for AF efficacy studies, Kv1.5 inhibitors may increase the ventricular effective refractory period (VERP) and heart rate corrected QT interval (QTc) interval in dogs. It is important to note that $I_{K_{ur}}$ has not been detected in human ventricular myocytes and therefore the same observation is unlikely in man. This is supported by the observation that 1 μ M diphenylphosphine oxide (DPO-1), a specific Kv1.5 blocker, has less of an effect on action potential duration (APD) recorded from human ventricular tissue³⁷ compared with APDs recorded from canine ventricular myocytes.³⁶ Rodent models should be used with caution because, unlike larger animals,³⁸ the transient-outward potassium current (I_{to}) contributes to late (Phase 3) repolarization and APD³⁹ and as such this species is unlikely to differentiate Kv4.2/3 from Kv1.5 blockers. The lack of human clinical data for selective Kv1.5 blockers means no conclusion can be drawn regarding which animal model is most predictive.

TABLE 1. Summary of Kv1.5 Inhibitor Patent Literature Showing Core Chemical Scaffold for Each Patent

Company	Publication	Year	Chemistry	Company	Publication	Year	Chemistry
Sanofi-Aventis	US6221866 ⁹⁷ WO0100573 ⁹⁸	2001 2001		Sanofi-Aventis	WO0244137 ⁹⁹	2002	
Sanofi-Aventis	WO02087568 ¹⁰⁰	2002		Sanofi-Aventis	WO0246162 ¹⁰¹	2002	
Sanofi-Aventis	WO02088073 ¹⁰² WO02100825 ¹⁰³	2002 2002		Sanofi-Aventis	WO0248131 ¹⁰⁴	2002	
Sanofi-Aventis	US6531495 ¹⁰⁵ WO0125189 ¹⁰⁶	2003 2001		Sanofi-Aventis	WO05025674 ¹⁰⁷ WO05084675 ¹⁰⁸	2005 2005	
Sanofi-Aventis	WO05025674 ¹⁰⁷ WO05084675 ¹⁰⁸	2005 2005		Sanofi-Aventis	WO06136305 ⁶²	2006	
Cardiome Pharma	WO05034837 ⁶⁷	2005		Epix	WO07047394 ¹⁰⁹	2007	
Bristol-Myers Squibb	WO0012077 ¹¹⁰	2000		Eli Lilly/Icagen	WO9937607 ¹¹¹	1999	
Bristol-Myers Squibb	WO0140231 ¹¹²	2001		Eli Lilly/Icagen	WO9962891 ¹¹³	1999	
Bristol-Myers Squibb	WO07027454 ¹¹⁴	2007		Eli Lilly/Icagen	WO9804521 ⁷¹	1998	

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TABLE 1. (continued) Summary of Kv1.5 Inhibitor Patent Literature Showing Core Chemical Scaffold for Each Patent

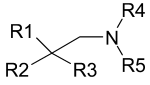
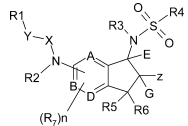
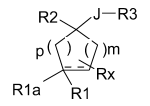
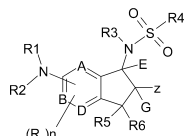
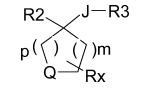
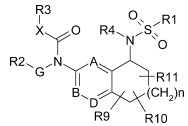
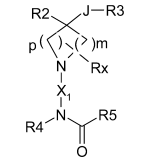
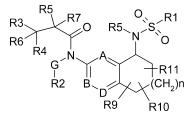
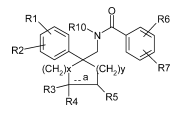
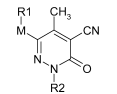
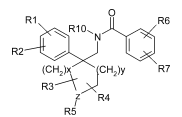
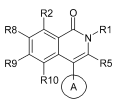
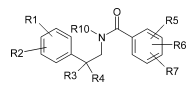
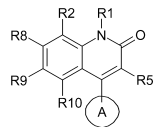
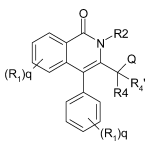
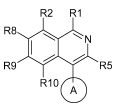
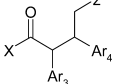
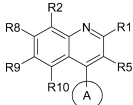
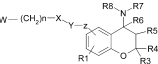
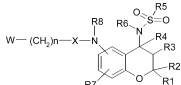
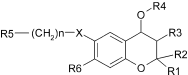
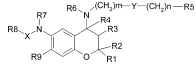
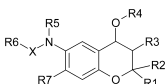
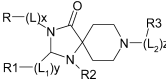
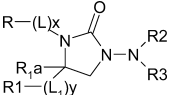
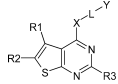
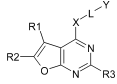
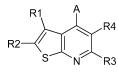
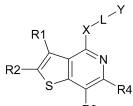
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BMS/Icagen	WO03063797 ¹¹⁶	2003		Icagen	WO02060874 ⁶⁹	2002	
BMS/Icagen	WO03088908 ¹¹⁷	2003		Icagen	WO0208183 ⁷⁵	2002	
BMS/Icagen	WO06073967 ¹¹⁸	2006		Icagen	WO02008191 ⁷⁶	2002	
Merck & Co.	WO0025770 ¹¹⁹	2000		Merck & Co.	WO9818475 ⁷⁹ WO9818476 ⁸⁰	1998 1998	
Merck & Co.	WO0025786 ¹²⁰	2000		Merck & Co.	WO05030726 ¹²¹ WO05030727 ¹²² WO05030791 ¹²³ WO05046578 ¹²⁴	2005 2005 2005 2005	
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Merck & Co.	WO02024655 ¹²⁷	2002		Merck & Co.	WO05030130 ¹²⁸	2005	

TABLE 1. (continued) Summary of Kv1.5 Inhibitor Patent Literature Showing Core Chemical Scaffold for Each Patent

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Nissan Chemical Industries	WO9804542 ¹³¹	1998		Nissan Chemical Industries	WO0058300 ¹³²	2000	
Nissan Chemical Industries	WO0121609 ¹³³	2001		Nissan Chemical Industries	WO0121610 ¹³⁴	2001	
—	—	—	—	Nissan Chemical Industries	WO0125224 ¹³⁵	2001	
Wyeth	WO07149873 ⁸⁸	2007		Wyeth	WO07149874 ⁸⁹	2007	
Xention	WO04111057 ¹³⁶	2004		Xention	WO05121149 ¹³⁷	2005	
Xention	WO06061642 ¹³⁸	2006		Xention	WO07066127 ¹³⁹	2007	

Aventis Pharma/Sanofi-Aventis

Aventis Pharma/Sanofi-Aventis has developed several novel nonselective Kv1.5 inhibitors from multiple chemically distinct series that include bisaryls, anthranilic acids, pyrrolidin-2-ones, piperidin-2-ones, and isothiazolidine-1,1-dioxides. Although many of the agents reported by Aventis Pharma/Sanofi-Aventis are mixed ion channel blockers, atrial selectivity and efficacy have been demonstrated in vivo. The atrial selective mechanism of action presumably stems from the compounds' propensity to block currents expressed solely or predominantly within the atria [ie, I_{Kur} (cardiac ultra-rapid delayed-rectifier potassium current), I_{to} and $I_{K(ACh)}$ (cardiac acetylcholine-modulated inward rectifier potassium current)]^{40,41} independent of I_{Kr} (cardiac rapid delayed rectifier potassium current) modulation.⁴²⁻⁴⁴ AVE0118 and AVE1231 have entered clinical development for the treatment of AF.

Bisaryls

AVE0118 inhibits hKv1.5 with an IC_{50} of 1.1 μ M.⁴⁵ AVE0118 inhibits hKv1.3, hKv2.1, hKv3.1, and hKv4.3 ion channels and pig atrial $I_{K(ACh)}$ with broadly similar potency to hKv1.5^{45,46} and displays a modest 10-fold selectivity over the cloned hERG (human ether-a-go-go related gene) channel ($IC_{50} \sim 10 \mu$ M). Good selectivity for Kv1.5 is demonstrated over other native cardiac currents I_{K1} (cardiac inward rectifier potassium current), I_{Ks} (cardiac slow delayed-rectifier potassium current), $I_{K(ATP)}$ (cardiac adenosine triphosphate-modulated inward rectifier potassium current), I_{CaL} (cardiac L-type calcium current)^{24,45} (Table 2). In vitro, AVE0118 (6 μ M) elevated the atrial action potential (AP) plateau and prolonged APD in human atrial tissue from patients with AF,⁴⁷ with higher concentrations (10–30 μ M) producing a positive inotropic effect in human atrial tissue from patients with SR

TABLE 2. Summary of Primary Ion Channel Pharmacology of Kv1.5 Inhibitors

	I _{Kur}	Kv1.5	I _{to}	Kv4.x± KChIP	I _{K(ΔCh)}	I _{Kr}
AVE0118 [Sanofi-Aventis]	1.1 μM, ¶ 1.3 μM§ ^{24,30}	1.1 μM, † 5.4–6.2 μM* ⁴⁵	1.8 μM¶ ²⁴	3.4 μM (Kv4.3+) ^{†45}	4.5 μM§ ⁴⁵	~10 μM** ⁴⁵
S9947 [Sanofi-Aventis]	71 nM, ‡ 955 nM ⁵⁷	417 nM, † 646 nM* ⁵⁷	<30% @ 10 μM‡ ⁵⁷	24% @ 10 μM (Kv4.3-)* ⁵⁷		
S20951 (Compound 4c) ¹⁰⁵ [Sanofi-Aventis]		1.4 μM* ¹⁰⁵				
AVE1231 [Sanofi-Aventis]	0.9–1.1 μM§ ^{54,59}	3.6 μM† ⁵⁴	3.3 μM§ ⁵⁹	5.9 μM (Kv4.3+) ^{†54}	8.4 μM§ ⁵⁴	~30 μM** ⁵⁴
AVE3295 [Sanofi-Aventis]	0.3 μM§ ⁵⁹	0.3 μM† ⁵⁹	0.5 μM§ ⁵⁹	5 μM (Kv4.3+) ^{†59}	2.4 μM§ ⁵⁹	
S0100176 [Sanofi-Aventis] Substituted pyrrolidin-2-ones and piperidin-2-ones (Compound 4) [Sanofi-Aventis]		700 nM* ^{61,140} 3.9 μM ⁶²				
Isothiazolidine-1,1-dioxides (Compound 9) [Sanofi-Aventis]		4.2 μM* ⁶²			7.8 μM** ⁶²	
Vernakalant/RSD1235 (& diastereomers) [Cardiome]	9 μM‡ ⁶⁴	13 μM† ⁶³	0.8–5 μM‡ ⁶⁴ 15 μM ⁶³	38 μM (Kv4.2-), 30 μM (Kv4.3-) ^{†63}	11 μM** ⁶³	
Imadazo Derivatives (Compound 1) [Cardiome]		4.8 μM† ⁶⁷		34 μM (Kv4.2-) ^{†67}		
C9356 [Cardiome]		4.4 μM† ²⁶		34 μM (Kv4.2-) ^{†26}		
ICAGEN-4 ⁷¹ [Icagen/Eli Lilly]	~1 μM‡ ⁷¹	~100– 160 nM† ^{71,72} 1.6 μM* ⁵⁸				
1R,2R-ICAGEN-4 [BMS/Icagen] Benzopyrans (Compound 9a) [BMS]		33 nM† ⁷² 57 nM† ⁷⁴				
DPO-1 [Merck & Co.]	30–80 nM‡ ³⁷	30–160 nM† ³⁷	NS @ 1 μM/ 8-fold‡ ³⁷			>20-fold I _{Kur} ** ³⁷
ISQ-1 [Merck & Co.]		110–324 nM† ^{81,82} 60 nM† ⁸¹				
Isoquinolinones (Compound 19) [Merck & Co.]		238 nM† ⁸²				
TAEA [Merck & Co.]		150 nM ⁸³				
Diisopropyl-2-pyridine-acetamides (Compound 10) [Merck & Co.]						
MSD-D ⁷⁹ (Compound D) [Merck & Co.]	80 nM‡ ⁷⁹	120 nM, † 500 nM* ^{58,79}				4.2% @ 3 μM** ⁷⁹
2,4 Disubstituted 1,2,3-triazoles (Compound 1f) [Procter & Gamble]		294 nM† ⁸⁴				>50 μM ⁸⁴
Tetrahydroindolone-derived semicarbazones (Compound 8i) [Procter & Gamble]		130 nM† ⁸⁵				21 μM† ⁸⁵
Tetrahydroindolone-derived carbamates (Compound 29) [Procter & Gamble]		21 nM† ⁸⁶				>30 μM† ⁸⁶
Tetrazole derivatives (Compound 2f) [Procter & Gamble]		330 nM† ⁸⁷				~15 μM† ⁸⁷
4-oxo-1,3,8triazaspiro[4,5]decanes ⁸⁸ (Example 4) [Wyeth]		151 nM† ⁸⁸				
1-N-amino-2-imidazolidonones ⁸⁹ (Compound 28) [Wyeth]		184 nM† ⁸⁹				

TABLE 2. (continued) Summary of Primary Ion Channel Pharmacology of Kv1.5 Inhibitors

hERG	I_{Ks}	$I_{Ca,L}$	I_{Na}	I_{K1}	$I_{K(ATP)}$	Other
~10 μM^\dagger ⁴⁵ NS @ 10 μM @ ⁵⁷	>>10 μM^{**45}	>>10 μM § NS @ 30 μM ¶ ^{24,46}		NS @ 10 μM^{**45} ~ 15% @ 10 μM ⁵⁷	>>10 μM^{**45}	No Selectivity Kv1.3/2.1/3.1 ^{*45,46}
	NS @ 30 μM^{**54}	26% @ 30 μM^{**54}	NS @ 30 μM^{**54}	NS @ 30 μM^{**54}	35% @ 30 μM^{**54}	
6% @ 10 μM ⁶⁰						2.3 μM^* (TASK-1) ⁶²
21–25 μM^\ddagger ^{63,64}		220 μM^{**63}	0.5–2 μM^\ddagger ⁶⁴ 9–107 μM^\ddagger ⁶³	>1 mM ^{**63,64}		0.4 μM^* (TASK-1) ⁶²
100 μM^\ddagger ⁶⁷			340 μM^\ddagger ⁶⁷			60 μM (Kv2.1) ^{†67}
97 μM^\ddagger ²⁶			335 μM^\ddagger ²⁶			60 μM (Kv2.1), [†] 168 μM (Kv3.1) ^{†26} ~100% @ 10 μM (Kv.13) ⁷¹
37% @ 10 μM ⁷² 35% @ 10 μM ⁷⁴			15% @ 10 μM ⁷²			~15-fold (Kv3.1) ^{*37}
	>20-fold I_{Kur}^{**37}			>20-fold I_{Kur}^{**37}		
5.3 μM^\ddagger 30 μM^\ddagger ^{81,82}		<20% @ 10 μM^\ddagger ⁸²	<20% @ 10 μM^\ddagger ⁸²		<20% @ 10 μM^\ddagger ⁸²	
30 μM^\ddagger ⁸²		<20% @ 10 μM^\ddagger ⁸²	<20% @ 10 μM^\ddagger ⁸²		<20% @ 10 μM^\ddagger ⁸²	
	13.6% @ 3 μM^{**79}			4.4% @ 3 μM^{**79}		10.1 μM (Kv1.3) ⁸⁴
		26 μM^\ddagger ⁸⁴				
		30 μM^\ddagger ⁸⁵				
		20 μM^\ddagger ⁸⁶				
		~23 μM^\ddagger ⁸⁷				
9.4 μM^\ddagger ⁸⁸		8 μM^\ddagger ⁸⁸				
10.3 μM^\ddagger ⁸⁹		30 μM^\ddagger ⁸⁹				

*, oocyte expression system voltage-clamp data; †, mammalian cell line expression system (eg, CHO, HEK, Ltk, etc) patch-clamp data; ‡, human patch-clamp data; §, pig patch-clamp data; ¶, dog patch-clamp data; ||, rat patch-clamp data; **, guinea-pig patch-clamp data; ††, FLIPR (Fluorometric Imaging Plate Reader) data; ‡‡, radioligand binding data; NS, no statistically significant effect.

TABLE 3. Summary of In Vivo Electrophysiologic Data in Animal Models

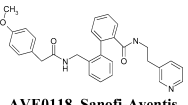
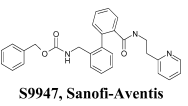
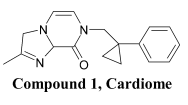
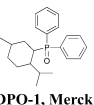
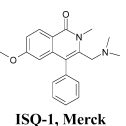
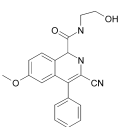
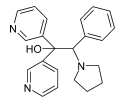
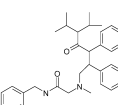
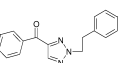
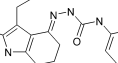
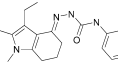
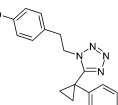
	Kv1.5 IC ₅₀	AERP	QT/QTc Interval	Efficacy	Orally Bioavailable	Development Status
 AVE0118, Sanofi-Aventis	1.1 μM ⁴⁵	**(+)- 56% LAERP, 20% RAERP at 1 mg/kg (IV), ⁴⁹ ‡‡(+)- 10%–30% at 3 mg/kg (IV) ⁵⁰ §§(+)- 35%–50% at 3 mg/kg (IV) ⁵⁰	**<3 ms (NS) at 1 mg/kg (IV) ⁴⁹ ‡‡>2 ms (NS) at 5 mg/kg ⁵⁰ §§>7 ms (NS) at 5 mg/kg ⁵⁰ ¶¶ NS at 0.5–10 mg/kg ⁵²	**Reduces (68%) AF vulnerability at 1 mg/kg (IV) ⁴⁹ §§Reduces AF vulnerability at 3 mg/kg (IV) ⁵⁰ §§Terminates AF (63%) at 5 mg/kg ⁵⁰	**No ⁴²	Phase 2a (discontinued)
 S9947, Sanofi-Aventis	417 nM ⁵⁷	**(+)- 55% LAERP, 15% RAERP at 3 mg/kg (IV) ⁴³	**NS at 3 mg/ kg (IV) ⁴³	**Reduces (100%) AF vulnerability at 3 mg/kg (IV) ⁴³	Not known	Not known
AVE1231, Sanofi-Aventis	3.6 μM ⁵⁴	**(+)- 30% at 3 mg/kg (oral and iv) ⁵⁴ ‡‡(+)- 27% at 3 mg/kg (IV) ⁴² §§(+)- 40% at 3 mg/kg (IV) ⁴²	‡‡NS at 3 mg/kg (IV) ⁴² §§NS at 3 mg/kg (IV) ⁴²	**Reduces (86%) AF vulnerability at 3 mg/kg (oral and iv) ⁵⁴ §§Reduces AF (54%–87%) vulnerability at 3 mg/kg (IV) ⁴²	**Yes ⁴²	Phase 1
AVE3295, Sanofi-Aventis	0.3 μM ⁵⁹	**(+)- 20% at 3 mg/kg (IV) ⁵⁹	**NS at 3 mg/kg (IV) ⁵⁹	**Reduces (66%) AF vulnerability at 3 mg/kg (IV) ⁵⁹	Not known	Not known
 Compound 1, Cardiome	4.8 μM ⁶⁷	‡(+)- 10% at 2.5 and 10 mg/kg (IV) ⁶⁷	Not known	‡Reduces (40%–50%, NS) AF duration at 2.5 and 10 mg/kg (IV)	Not known	Not known
 DPO-1, Merck	30–160 nM ³⁷	‡‡(+)- 15% at 10 mg/kg (IV) ⁷⁷ (+)- 42% at 12 mg/kg ⁷⁷	‡‡>16 ms (NS) at 10 mg/kg (IV) ⁷⁷	‡Terminates (100%) AFI at 5.5mg/kg (mean dose, iv) ⁷⁸	Not known	Not known
 ISQ-1, Merck	110–324 nM ^{81,82}	*(+)- 16% at 30 μg/kg/min (IV) ³⁴ ‡(+)- 13% at 2.5 mg/kg (mean iv dose) ³⁴ No effect at 0.03 to 1 mg/ kg (IV) ⁸² ‡‡(+)- 17% at 3 mg/kg (IV) ³⁴ (+)- 36% at 12 mg/kg	*>29 ms (NS) at 30 μg/kg/min (IV) ³⁴ ‡Not known NS 0.03 to 1 mg/kg (IV) ⁸² ‡‡>20ms (NS) at 3 mg/kg (IV) ³⁴	‡Terminates (83%) AFI at 2.5 mg/kg (mean dose, iv) ³⁴ Terminates (57%) AF at 0.03 to 1 mg/kg (IV) ⁸²	No ⁸¹	Not known
 Compound 19, Merck	60 nM ⁸¹	*(+)- 14% at 100 nM plasma conc. ⁸¹ (+)- 30% at 5 μM plasma conc. ⁸¹	Not known	Not known	Yes ⁸¹	Not known

TABLE 3. (continued) Summary of In Vivo Electrophysiologic Data in Animal Models

	Kv1.5 IC ₅₀	AERP	QT/QTc Interval	Efficacy	Orally Bioavailable	Development Status
 TAEA, Merck	238 nM ⁸²	*(+), 16% at 0.3 mg/kg (IV) ⁸² No effect 0.01 to 0.3 mg/kg (IV) ⁸²	NS at 0.01 to 0.3 mg/kg ⁸²	Terminates (67%) AF (at multiple doses, iv) ⁸²	Not known	Not known
 Compound 10, Merck	150 nM ⁸³	*(+), 15% 0.45 µg/kg/min (IV) ⁸³	Not known	Not known	Not known	Not known
 Compound 1f, P&G	294 nM ⁸⁴	**(+), 12% at 30 mg/kg (IV) ⁸⁴	Not known	Not known	Not known	Not known
 Compound 8i, PG	130 nM ⁸⁵	**(+), 28% at 10 mg/kg (IV) ⁸⁵	Not known	Not known	Not known	Not known
 Compound 29, P&G	21 nM ⁸⁶	Not known	Not known	Not known	Not known	Not known
 Compound 2f, P&G	330 nM ⁸⁷	**(+), 17% at 10 mg/kg (IV) ⁸⁷	Not known	Not known	Not known	Not known
XEN-D0101, Xention	241 nM (unpublished data)	*(+), 22%–49% at 3 mg/kg (IV) ¹⁴¹ †(+), 45% at 3 mg/kg (IV) ¹⁴²	* >3 ms (NS) at 10 mg/kg (IV) ¹⁴¹ † >15 ms (NS) at 3 mg/kg (IV) ¹⁴²	*Reduces AF duration at 1 mg/kg (IV) ¹⁴¹ †Reduces AF duration and vulnerability at 1 mg/kg (IV) ¹⁴²	Not known	Phase 1

* , dog (normal); †, dog (tachypaced AF); ‡, dog (atrial flutter); §, dog (vagab AF); ¶, dog (aconitine-induced AF); ||, dog (AF/ heart failure); **, Anesthetized pig; ††, African green monkey; ‡‡, goat; §§, goat (tachypaced AF); ¶¶, Chronic complete atrioventricular block dog model; |||, rat; NS, no statistically significant effect; IV, intravenous administration.

and AF.²⁴ Similarly, AVE0118 prolonged APD₃₀ and elevated the plateau potential in canine right atrial (RA) myocytes at concentrations of 1–100 µM while shortening APD₅₀ and ADPD₉₀ in right ventricular (RV) myocytes. The effect of AVE0118 on human ventricular action potential profile in vitro has not been reported. In Langendorff-perfused rabbit hearts where the right atrium was dilated to shorten the atrial effective refractory period (AERP) and increase AF vulnerability, AVE0118 at the maximum dose (10 µM) prolonged right AERP (RAERP) by 85%. Perfusion of the same concentration reduced AF vulnerability to 0 and in a separate group

terminated sustained AF in 5/6 hearts to SR by reducing the signal complexity.⁴⁸ Thus, in vitro at 1- to 10-fold above the IC₅₀ for Kv1.5, AVE0118 delays atrial but not ventricular repolarization and is able to prevent and terminate AF.

The in vivo electrophysiologic effects and antiarrhythmic properties of AVE0118 have been well-characterized in a number of animal models (Table 3). In the anesthetized pig, intravenous administration of 1 mg/kg AVE0118 preferentially increased the LAERP (left AERP) > RAERP (56% versus 20% at 3.3Hz) and completely prevented left atrial vulnerability (LAV) to extrastimulus-induced AF.^{44,49} At this dose

AVE0118 had no effect on QT/QT_c interval.⁴⁹ In contrast, I_{Kr} blockers preferentially prolonged RAERP > LAERP and the QT_c interval and failed to reduce LAV.^{43,44} Thus, it is clear that AVE0118 has a different mechanism of action to I_{Kr} blockers. In a conscious goat pacing-induced tachycardia model of persistent AF, intravenous administration of 3 mg/kg AVE0118 was more effective in increasing the AERP in AF animals (>35%–50%) compared with control animals (>10%–30%) and reduced AF vulnerability by 68%.⁵⁰ Furthermore, intravenous administration of 5 mg/kg AVE0118 (peak plasma concentration 10.22 μM) terminated persistent AF in 5/8 goats and had no effect on the QT interval or atrial conduction velocity.⁵⁰ As in human atrial tissue, AVE0118 was able to restore atrial contractility following cardioversion in the goat persistent AF model.²³ An increase in atrial contractility may increase the blood flow velocity in the left atrium (LA) following cardioversion, resulting in lower risk of thrombus formation and stroke, and it may be a Kv1.5 blocker “class effect.”^{23,51} In the canine chronic complete AV block (CAVB) model, in which animals are susceptible to TdP, a range of AVE0118 doses producing plasma concentrations that reached 12.7 μM did not increase the QT_c interval, cause TdP, or prevent dofetilide-induced TdP.⁵² Complementary to the in vitro data, AVE0118 selectively increases the AERP with minimal effects on ventricular function.

AVE0118 is poorly soluble,^{48,49} undergoes rapid first-pass hepatic metabolism,⁵³ and has a short half-life in dog and pig (intravenous administration, T_{1/2} = 0.2–0.4 hours^{52,54}). AVE0118 has not progressed past Phase 2 clinical development for AF⁵⁵ and is currently in preclinical development for obstructive sleep apnea via a nasal route.⁵⁶ No Phase 2 clinical data for AVE0118 have been published to date.

S9947 inhibits hKv1.5 (IC₅₀ value 417 nM), in a strong positive frequency-dependent manner and also inhibits human I_{Kur} (IC₅₀ value 77 nM)^{57,58} (Table 2). S9947 does not inhibit hERG heterologously expressed in oocytes at 10 μM. Similar to AVE0118, S9947 (intravenous administration at 1 and 3 mg/kg) preferentially increased LAERP (~20%–55% LAERP and 10%–15% RAERP) and abolished LA vulnerability at the higher dose in the anesthetized pig without prolonging the QT_c interval.^{43,44} Pharmacokinetic properties, efficacy in AF models, and the development status of S9947 are unknown. Similar observations in pig were also reported for the Kv1.5 blocker S20951.^{43,44}

Anthranilic Acids

AVE1231, an anthranilic acid (structure not disclosed), blocked hKv1.5 and I_{Kur}, I_{to} and I_{K(ACh)} with IC₅₀ values of 3.6, 0.9, 3.3, and 8.4 μM, respectively; displayed superior hERG selectivity to AVE0118 (IC₅₀ ~30 μM; see Table 2); and had no effect on guinea pig papillary muscle APD₉₀ at 30 μM.⁵⁴ At the maximum-studied oral dose in the anesthetized pig, AVE1231 (3 mg/kg) produced a 30% increase in LAERP at the fastest pacing rate and reduced LAV by 86% with no effect on the QT/QT_c, R-R intervals or the QRS complex.⁵⁴ An almost identical effect was observed following intravenous administration in the anesthetized pig at 3 mg/kg.^{54,59} In a conscious pacing-induced tachycardia goat model of persistent AF, intravenous administration of 3 mg/kg AVE1231 was more effective in

increasing the AERP in AF animals (~40%) compared with control animals (~27%) and had no effect on the QT_c interval.^{42,54} However, in contrast to AVE0118, AVE1231 was less effective in reducing LAV following remodeling and did not increase the LAERP in a reverse-rate-dependent fashion in this goat model.⁴² Unlike AVE0118, AVE1231 was shown to be orally active in the pig model.⁵⁴ AVE1231 is currently in Phase 1.⁵⁶

AVE3295 (structure not disclosed) inhibits pig I_{Kur}, I_{to} and I_{K(ACh)} with a IC₅₀s of 0.3, 0.5, and 2.4 μM, respectively⁵⁹ (Table 2). Although a more potent ion channel blocker than the structurally similar AVE1231, AVE3295 was less effective in vivo, producing smaller changes in anesthetized pig LAERP and LAV at an identical dose (Table 3).⁵⁹ At 3 mg/kg intravenous AVE3295 produced no significant effect on the pig QT interval.

S0100176 (Compound 3i⁶⁰) is a positive frequency-dependent open channel blocker of hKv1.5 (IC₅₀ value 700 nM in oocytes), >10-fold selective for hERG (see Table 2), and orally bioavailable (43%) in the rat.^{60,61} No in vivo electrophysiology has been published for this compound and its development status is unknown.

The Aventis (nonselective) Kv1.5 inhibitors previously mentioned appear to have a “class effect” independent of I_{Kr} modulation. Preferential action on the LAERP and efficacy in animal models support the possibility of Kv1.5 inhibitors as effective in both the prevention and termination of AF without producing undesirable ventricular effects.

Substituted Pyrrolidin-2-Ones, Piperidin-2-Ones, and Isothiazolidine-1,1-Dioxides

Substituted pyrrolidin-2-ones, piperidin-2-ones, and isothiazolidine-1,1-dioxides have been reported as mixed ion channel inhibitors (eg, Compound 4, hKv1.5 IC₅₀ 3.9 μM and 2-pore acid-sensitive K⁺ channel [TASK-1; IC₅₀ 2.3 μM; Compound 9, hKv1.5 IC₅₀ 4.2 μM, TASK-1 IC₅₀ 0.4 μM and I_{K(ACh)} IC₅₀ 7.8 μM⁶²; Table 2). Although all 3 ion channels are expressed in the human atria, the pharmacodynamic benefit of modulating these 3 ion channels is unknown because no AF efficacy data have been presented. It was noted that the TASK-1 modulating activity of these compounds may be mechanistically important in several other noncardiac diseases (eg, sleep apnea).⁶²

Cardiome/Astellas Pharma

Vernakalant hydrochloride (RSD1235) developed by Cardiome (later Astellas) inhibits hKv1.5 and human I_{Kur} in a use- and frequency-independent fashion with an IC₅₀ of 13 μM (0.25–20 Hz) and 9 μM (0.1–3Hz), respectively.^{63,64} However, at depolarized resting membrane potentials and high frequencies vernakalant preferentially inhibits hNav1.5⁶⁴ and I_{to} (Table 2)^{63,64} over hKv1.5. A mechanism for chamber selectivity of the Na⁺ channel blockers, ranolazine and lidocaine, has been proposed to be consequent on different Na⁺ channel inactivation characteristics in, respectively, the atria and the ventricles⁶⁵ and this may in part explain vernakalant's atrial selectivity. As a preferential Na⁺ channel blocker, vernakalant is outside the remit of this review⁶⁶; however, it is noteworthy because in December 2007 a U.S. Food and Drug Administration expert advisory panel

recommended approval of vernakalant (Kynapid) for rapid cardioversion of recent-onset AF.

Imadazo Derivatives

Compound 1 is a modest inhibitor of hKv1.5 (IC_{50} value 4.8 μ M) that is selective for hKv1.5 over several nontarget cardiac currents: hERG (20-fold), Kv4.2 (7-fold), Kv2.1 (12-fold), and Nav1.5 (~60-fold).⁶⁷ Intravenous administration of 2.5 and 10 mg/kg Compound 1 marginally reduced AF duration (~40%) and increased the AERP (10%) in the dog pacing-induced AF model. In another study, Compound 1 did not significantly increase the pulmonary artery pressure at 25 mg/kg in rat, suggesting that, in contradiction to previously reported studies, Kv1.5 is not functionally important in pulmonary artery smooth muscle cells.⁶⁸ C9356 (structure and chemical series undisclosed) is a Kv1.5 blocking compound that displays identical pharmacology to Compound 1 (Table 2).²⁶ It is unclear if Cardiome is actively pursuing Kv1.5 as a target for AF.

Icagen/Eli Lilly/Bristol-Myers Squibb

In separate collaborations with Eli Lilly and Bristol-Myers Squibb (BMS), Icagen has developed several novel Kv1.5 inhibitors from multiple distinct chemical series that include indanes, tetralins, benzocycloheptanes, thiazolidinones, metathiazanones, and dihydropyrimidines (see Tables 2 and 3 for key compound examples). A clinical development candidate was identified by the Icagen-BMS program and progressed to a Phase 1 proof-of-concept trial. However, in December 2005 Icagen/BMS announced discontinuation of the trial because of slow enrollment. It has also been reported that clinical trials of exemplified Compound 25⁶⁹ were halted because of poor solubility and oral bioavailability.⁷⁰ It is unclear if these 2 trials are one and the same.

Indanes

In 1998 Icagen and Eli Lilly published work relating to a series of indane compounds. Compound 4 (ICAGEN-4⁷¹) is an open channel, frequency-dependent inhibitor of hKv1.5, blocking the hKv1.5 current and human I_{Kur} with IC_{50} s of 100–160 nM and 1 μ M, respectively, and capable of prolonging the human atrial APD in vitro at 1 μ M.^{58,71,72} This compound was shown to inhibit human T-cell proliferation at 10 μ M as a result of off-target activity through Kv1.3.⁷¹ Further Icagen patents have expanded on the indane series revealing compounds that inhibit hKv1.5 current by 20% to 66% at 100 nM.^{69,73} Using ICAGEN-4 as a template, Icagen and BMS have produced a collection of aryl sulphonamido indanes with potency against hKv1.5 ranging from 33 to 880 nM.⁷² The most potent compound (*1R,2R* diastereomer of ICAGEN-4) displayed good selectivity over hERG, hNav1.5, and rat pituitary Ca^{2+} current (Table 2) but was not orally bioavailable in the rat and dog. Improved solubility and pharmacokinetic profiles would be required to allow these compounds to progress to the clinic.

Benzopyrans

BMS replaced the indane scaffold (ICAGEN-4⁷¹) with a benzopyran scaffold yielding compounds with an IC_{50} s for hKv1.5 ranging from 57 nM to >1 μ M and excellent selectivity over hERG (100–300-fold)⁷⁴ (Compound 9a,

Table 2). No in vivo electrophysiology has been published for these compounds and their development status is unknown.

Tetrahydronaphthalenes

In 2002 Icagen published 2 patents detailing compounds that potentially inhibit both the peak and the steady-state hKv1.5 current at 100 nM. AP voltage-clamp studies using a human atrial AP waveform applied to hKv1.5-expressing cells showed that compounds with a “slow-off rate” (those that inhibited peak hKv1.5 current) were more effective in blocking the hKv1.5 current during the human atrial AP waveform and thus were predicted to be more effective antiarrhythmics.^{75,76} However, no in vivo data are presented to support this hypothesis. From the data presented it is unclear if the compounds have a slow off rate or very rapid on rate.

Because very little in vivo data are available for the Icagen/Eli Lilly/BMS compounds described previously, it is difficult to determine the development status of their Kv1.5 inhibitor programs.

Merck

Merck has developed several novel Kv1.5 inhibitors from multiple distinct chemical series that include diphenylphosphine oxides, isoquinolinones, triarylethanolamines, and diisopropylamides. It is not known if Merck has selected a development candidate from 1 of these chemical series.

Diphenylphosphine Oxides

DPO-1, a potent frequency-dependent inhibitor of hKv1.5 (IC_{50} value 30 nM) and human I_{Kur} (IC_{50} value 30 nM),³⁷ is selective for Kv1.5/ I_{Kur} over several nontarget cardiac currents: I_{to} (8-fold), I_{K1} (20-fold), I_{Kr} (20-fold), and I_{Ks} (20-fold).³⁷ An atrial-selective mechanism has been demonstrated ex vivo; DPO-1 (at 1 μ M) increased the duration of APs recorded from dissociated human atrial myocytes (increases APD_{50} by 120% and APD_{90} by 25%) and had no effect on the duration of APs recorded from ventricular myocytes.³⁷ The in vivo cardiac electrophysiologic profile of DPO-1 has been reported for rat and African green monkey: DPO-1 at 12 mg/kg (plasma concentration ~8 μ M) increased the AERP and VERP by 42% and 64%, respectively, in rat; and at 10 mg/kg (plasma concentration 5 μ M) selectively increased the AERP by 15% in monkey.⁷⁷ DPO-1 terminated atrial flutter in 6/6 dogs at a mean intravenous dose of 5.5 mg/kg \pm 2 mg/kg and selectively increased the AERP by 15%.⁷⁸ Mean pharmacodynamic and pharmacokinetic data were not reported for individual dose groups; however, in the example that was cited, DPO-1 terminated AFI at 10 mg/kg but not at 1 and 3 mg/kg. Although atrial selectivity and antiarrhythmic activity have been demonstrated, DPO-1 is unlikely to enter drug development if it is not orally bioavailable (only intravenous data have been reported). DPO-1's pharmacology and pharmacodynamic effects are also reported elsewhere.^{79,80}

Isoquinoline-3-Nitriles

Limited electrophysiology and pharmacokinetic data are available for isoquinoline-3-nitrile (ISQ-1; hKv1.5 IC_{50} value 110–324 nM, 30- to 50-fold selective for hKv1.5 over hERG, and poorly bioavailable in rat).^{81,82} Comprehensive in vivo

cardiac electrophysiology studies have been performed with ISQ-1 in multiple species: ISQ-1 at 12 mg/kg (plasma concentration $\sim 12 \mu\text{M}$) increased rat AERP and VERP by 36% and 33%, respectively; at 3 mg/kg (plasma concentration $20 \mu\text{M}$) selectively increased monkey AERP by 17%;³⁴ and in dog stable drug plasma concentrations of approximately $0.3 \mu\text{M}$ selectively increased the AERP by 16%.³⁴ No effect on the QTc interval was observed at peak plasma concentrations of $1.8\text{--}2.0 \mu\text{M}$ and $20.3 \mu\text{M}$ in the dog and African green monkey, respectively. ISQ-1 terminated atrial flutter in 5/6 dogs at a mean intravenous dose of $2.5 \text{ mg/kg} \pm 0.5 \text{ mg/kg}$ and selectively increased the AERP by 13%.³⁴ As with DPO-1, this study did not report individual dose group pharmacodynamic and pharmacokinetic information. ISQ-1 also terminated atrial fibrillation in 4/7 conscious dogs with underlying heart failure at all intravenous doses tested (0.03 to 1.0 mg/kg) without causing significant changes in the AERP (plasma concentration reached $1.3 \mu\text{M}$). The reason for the lack of drug-related AERP changes in the heart-failure dogs is unknown. ISQ-1 is unlikely to enter clinical development because of its poor oral bioavailability.³⁷ However, both DPO-1 and ISQ-1 are Kv1.5 selective compounds that demonstrate atrial selectivity and efficacy in animal models without undesired ventricular effects.

The authors describe DPO-1 and ISQ-1 as investigational molecules that have contributed to Kv1.5 target validation.

Compound 19 has similar electrophysiologic properties to DPO-1 and ISQ-1 (hKv1.5 IC_{50} value 60 nM); drug plasma concentration of approximately $5 \mu\text{M}$ increased the AERP and VERP by 30% and 35%, respectively, in rat, and drug plasma concentrations of $\sim 0.1 \mu\text{M}$ selectively increased the AERP by 14% in dog.⁸¹ It is important to note that Compound 19 has much improved oral bioavailability compared to ISQ-1.⁸¹ Efficacy data in AF/AFI animal models and extensive cardiac ion channel selectivity data have not been reported for this compound. Based on the fact that AERP changes observed in dog were similar to DPO-1 and ISQ-1, one would reasonably expect this compound to be effective in similar arrhythmia models.

Triarylethanolamines

Triarylethanolamine (TAEA) is a potent inhibitor of hKv1.5 (IC_{50} value 238 nM)⁸² that terminated atrial fibrillation in 4/6 conscious dogs with underlying heart failure at all intravenous doses tested (0.01 to 0.3 mg/kg). Like ISQ-1, TAEA (drug plasma levels up to $2 \mu\text{M}$) did not produce any detectable changes in the AERP in heart-failure dogs. In normal dogs, significant AERP increases were observed at 4-fold lower drug plasma levels.⁸²

Diisopropylamides

Compound 10 is a potent inhibitor of hKv1.5 (IC_{50} value 150 nM) that selectively increased dog AERP by 15% (plasma concentration 20 nM).⁸³ Efficacy data in clinically relevant animal models, pharmacokinetic data (oral bioavailability, half-life), and noncardiac safety data have not been reported for this compound.

In summary, DPO-1, TAEA, and Compound 10 are attractive development candidates if orally bioavailable, and

Compound 19 is an attractive development candidate if efficacy is demonstrated in AF models. Taken together, the data presented for these compounds provide good evidence for the potential of selective Kv1.5 inhibitors to be safe and effective in the treatment of AF.

Procter and Gamble

Procter and Gamble have developed several novel Kv1.5 inhibitors from multiple chemical series that include triazoles, tetrahydroindolone-derived semicarbazones, tetrahydroindolone-derived carbamates, and tetrazoles.

2,4 Disubstituted 1,2,3-Triazoles

Compound 1f is a potent inhibitor of hKv1.5 (IC_{50} value 294 nM) that is selective for Kv1.5 over hERG (170-fold) and L-type calcium currents (88-fold) and at 30 mg/kg (intravenous administration) selectively increased pig AERP by 12%.⁸⁴

Tetrahydroindolone-Derived Semicarbazones

Compound 8i is a potent inhibitor of hKv1.5 (IC_{50} value 130 nM) that at 10 mg/kg (intravenous administration) selectively increased the pig AERP by 28%.⁸⁵

Tetrahydroindolone-Derived Carbamates

Compound 29 is a potent inhibitor of hKv1.5 (IC_{50} value 21 nM) that is at least 1000-fold selective for Kv1.5/ I_{Kur} over hERG and L-type calcium currents.⁸⁶

Tetrazole Derivatives

Compound 2f is a potent inhibitor of hKv1.5 (IC_{50} value 330 nM) that is at least 50-fold selective for Kv1.5 over hERG and L-type calcium currents, and at 10 mg/kg (intravenous administration) selectively increased the pig AERP by 17%.⁸⁷

Efficacy data in clinically relevant atrial fibrillation animal models, pharmacokinetic data (oral bioavailability, half-life), and noncardiac safety data have not been reported for any of the preferred Kv1.5 inhibitors described by Procter & Gamble. Demonstration of oral bioavailability and efficacy in AF models will clearly need to be demonstrated before any of these compounds can advance toward development.

Wyeth

Two patents relating to 4-oxo-1,3,8-triaza-spiro[4,5]decanes⁸⁸ and 1-*N*-amino-2-imidazolidonones⁸⁹ and their derivatives as Kv1.5 blockers have recently been published by Wyeth: Compound 4⁸⁸ inhibits hKv1.5 (IC_{50} value 151 nM) and is >50- and 60-fold selectivity over $I_{\text{Ca,L}}$ and hERG, respectively; and Compound 28⁸⁹ inhibits hKv1.5 (IC_{50} value 184 nM) and is >160- and 50-fold selectivity over $I_{\text{Ca,L}}$ and hERG, respectively. No in vivo electrophysiology data have been published for these compounds and their development status is unknown.

Xention

Xention has developed several novel Kv1.5 inhibitors from multiple chemical series. Xention's Kv1.5 development candidate, XEN-D0101, is currently in Phase 1.⁹⁰

XEN-D0101

XEN-D0101 inhibits hKv1.5 and human atrial I_{Kur} with an IC_{50} of 241 and 154 nM , respectively (data unpublished).

Intravenous doses of XEN-D0101 selectively increased the AERP in a rate-dependent and dose-dependent manner in normal dogs (eg, 3 mg/kg XEN-D0101 increased AERP 49% at 200 ms basic cycle length and by 22% at 360 ms basic cycle length⁹¹), and in dogs with atrial tachycardia-induced electrical remodeling, XEN-D0101 selectively increased AERP by 25% at 1 mg/kg and 45% at 3 mg/kg.⁹² XEN-D0101 did not increase the QTc interval at the highest dose in either dog AF model. XEN-D0101 significantly reduced the mean AF duration in normal dogs and atrial-tachypaced dogs and significantly reduced AF vulnerability in atrial tachypaced dogs.^{91,92} No ion channel selectivity, pharmacokinetic, or safety data have been reported for XEN-D0101.

CONCLUSIONS

This review highlights the wealth of new and novel Kv1.5 chemistry that is being developed by industry. However, the value of many of these new compounds is limited because these compounds have yet to demonstrate the desired druglike characteristics of Kv1.5 selectivity over other ion channels; atrial selectivity (in vivo); efficacy in clinically relevant AF animal models; oral bioavailability; safety in animals following repeat dosing; and, crucially, clinical efficacy and safety. As such, the accolade of “first in class” is still to be achieved. The most advanced Kv1.5 inhibitors reported are considered to be the following:

- AVE0118, which reached Phase 2, although the results of this trial have not been reported. AVE0118 is a mixed ion channel inhibitor that is atrial selective in vivo and efficacious in multiple AF animal models. The physicochemical and pharmacokinetic properties of AVE0118 may limit the progression of this drug candidate for AF treatment.
- AVE1231 has similar pharmacology and pharmacodynamic effects to AVE0118 but has the advantage of being orally effective. This drug candidate is currently in Phase 1 for AF. The selection of a second clinical candidate, with similar mixed ion channel pharmacology (to AVE0118), is indicative of continuing confidence in target validity following a clinical efficacy Phase 2 trial.
- XEN-D0101 has entered Phase 1 and is being developed for the prevention of AF. Although XEN-D0101 has been shown to be atrial selective and efficacious in multiple dog AF models, its selectivity for Kv1.5 over noncardiac ion channels has not been reported.
- Icagen/BMS were planning to assess an unidentified Kv1.5 clinical development candidate in a Phase 1b pharmacodynamic study. However, in December 2005 Icagen/BMS announced discontinuation of the trial because of slow enrollment. The status of this development candidate and program is unknown.

The fact that the drug development candidates described here have entered clinical development suggests that pharmacologic modulation of Kv1.5 in humans is widely seen to be an important candidate drug target. It remains to be demonstrated that Kv1.5 inhibitors are atrial selective and well-tolerated in a clinical setting. The recruitment criteria for clinical efficacy studies require careful consideration for Kv1.5 inhibitors.

Kv1.5 inhibitors have been shown to be very effective in animal models of AFL, vagal AF, sustained AF (following atrial high-rate pacing), and animals with AF and heart failure. In disease models and tissue a number of compounds display increased efficacy potentially as a result of ion channel remodeling in AF^{93–96} that may influence the functional role of Kv1.5 in atrial repolarization. The predictive value of these models is yet to be demonstrated. These observations should be taken into account when designing the recruitment criteria for Phase 2 clinical studies with Kv1.5 inhibitors.

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