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### Review

# Challenges of small molecular modulators with potassium current channel isoform Kv1.5

Zefeng Zhao<sup>a</sup>, Songsong Ruan<sup>a</sup>, Xiaoming Ma<sup>a</sup>, Qian Feng<sup>a</sup>, Zhuosong Xie<sup>a</sup>, Zhuang Nie<sup>a</sup>, Peinan Fan<sup>a</sup>, Mingcheng Qian<sup>c, d</sup>, Xirui He<sup>e</sup>, Shaoping Wu<sup>a, \*</sup>, Yongmin Zhang<sup>a, b</sup> and Xiaohui Zheng<sup>a</sup>

<sup>a</sup>School of Pharmacy;Key Laboratory of Resource Biology and Biotechnology in Western China, Ministry of Education; Biomedicine Key Laboratory of Shaanxi Province; Northwest University, 229 Taibai Road, Xi'an 710069, China;

<sup>b</sup>Sorbonne Université, InstitutParisien de ChimieMoléculaire, CNRS UMR 8232, 4 place Jussieu, 75005 Paris, France;

<sup>c</sup> Department of Medicinal Chemistry, School of Pharmaceutical Engineering and Life Science, Changzhou University, Changzhou 213164, Jiangsu, China;

<sup>*d*</sup> Laboratory for Medicinal Chemistry, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium;

<sup>e</sup> Department of Bioengineering, Zhuhai Campus of Zunyi Medical University, Zhuhai, 519041, China.

\* Correspondence: wushaoping@nwu.edu.cn.

**Abstract :** The voltage-gated potassium channel Kv1.5 mediating the cardiac ultra-rapid delayed-rectifier ( $I_{Kur}$ ) current in human cells reveals crucial role in atrial fibrillation. Therefore, the design of selective Kv1.5 modulators should be a key work for the treatment of pathophysiological conditions involving Kv1.5 activity. This review summarized the progresses of the molecular structures and functionality of different types of Kv1.5 modulators, mainly including clinical cardiovascular drugs and a number of active natural products by a summarization of currently widely used 91 compounds. Furthermore, we also discussed the contributions of Kv1.5 and regulation of the Structure-Activity Relationship (SAR) of synthetic Kv1.5 inhibitors, in human pathophysiology. SAR analysis is regarded as a useful strategy in the structural elucidation relating to the characteristics that improve compound-targeting Kv1.5. Herein, we present the previous works regarding the structural, pharmacological and SAR information of Kv1.5 modulator, through which, to assist the identify and design of potent and specific Kv1.5 inhibitors in the treatment of diseases involving Kv1.5 activity.

Keywords: Potassium channel; Kv1.5; KCNA5; Modulators; SAR;

# Highlights

• This review summarized the progress in models and mechanisms of multiple

existing Kv1.5 modulators with a total for 96 compounds.

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- A preliminary discussion about the Structure-Activity Relationship (SAR) of synthetic Kv1.5 inhibitors was also summarized.
- This review provides evidence to design potent and selective Kv1.5 inhibitors for target specific treatment of diseases involving Kv1.5 activity.

The voltage-gated potassium channel Kv1.5 mediating  $I_{Kur}$  current in cells [1] is an attractive familial atrial fibrillation (AF) type 7 drug target because it is selectively expressed in human in atria but not in the ventricles of human cells [2]. AF is the most common cardiac arrhythmia facing physicians, afflicting 13% of men and 11% of women over 85 years of age. In atrial tissue from AF donors, inhibition of  $I_{Kur}$  extends the repolarization phase of the atrial cardiac action potential to provide desirable antiarrhythmic effects without the risk of drug-induced *torsade de pointes*. It is noteworthy that loss-of function Kv1.5 mutations have been associated with AF, and many companies are exploring  $I_{Kur}$  modulators for treatment of AF [3].

The protein of Kv1.5 is encoded by KCNA5 gene with length of 602 amino acids in the sequence in mouse (Unitprot Entry: Q61762) and rat (Unitprot Entry: P19024) and 613 amino acids in the sequence in human (Unitprot Entry: P22460). According to the Basic Local Alignment Search Tool (BLAST) result, the sequence of Kv1.5 is similar to homology targets Kv1.1, Kv1.2 and Kv1.3 in majority regions and the different regions mainly focus on the start and end terminals of sequence (Figure **1C and Figure 1D**). The Kv1.5 channel belongs to the *Shaker-type* voltage-gated K<sup>+</sup> channel family and comprises four pore-forming  $\alpha$ -subunits, each containing six transmembrane segments, named S1-S6 [4, 5]. A pore region formed between the pore helix and S6 domain of each subunit contains the selectivity filter through which K<sup>+</sup> ions flow across the plasma membrane [6, 7]. Up to now, the structure of Kv1.5 protein is still waiting for the identification, but alanine-scanning mutagenesis and homologous modeling studies have given us some amino acids including Thr 479, Ile 502, Val 505, Ile 508 and Val 512 that reside within the deep pore (Thr479-Val481) and lower S6 (Cys500-Val512) regions as putative binding sites for the open channel blockers [8-13] (Figure 1B), which not only helps us understand the drug targets more comprehensively, but also saves the time for the

development of potential clinical candidates in the future. In this perspective, we highlight recent advances in the discovery of small molecular as the modulators of Kv1.5 and discuss the SAR studies of currently synthetic Kv1.5 inhibitors.



**Figure 1.** (**A**) Schematic representation of hKv1.5  $\alpha$ -subunit with the sequence of S6 region listed; (**B**) Homologous model of Kv1.5 (Q61672) with the range of 67.2% for sequence of Kv1.5 getting from the SWISS-MODEL database, some of the residues are slightly different with the contents from published literatures; (**C**) BLAST result of KCNA5\_HUMAN (P22460) obtaining from NCBI BLAST+ database; (**D**) Sequence alignment between KCNA1\_HUMAN (Q09470), KCNA3\_HUMAN (P22001), KCNA2\_HUMAN (P16389) and KCNA5\_HUMAN (P22460) acquiring from ESPript database.

## Summarization of models and mechanisms of Kv1.5 modulators

Up to date, various kinds of Kv1.5 modulators have been disclosed, herein, we summarize the molecular structures and functionality of different types of Kv1.5

modulators with their chemical structure as follows (**Table 1**) (**Figure 2**). As shown in the **Table 1**, the existing Kv1.5 modulators can be divided into four categories: clinical cardiovascular drugs (**1-14**), other clinical drugs (**15-28**), drugs in development (**29-37**) and natural products (**38-56**). With the development of pharmacology, more and more experiment models including rats, HEK cells, CHO cells, *Xenopus laevis oocytes* and Ltk<sup>-</sup> cells have been used to evaluate the effect of Kv1.5 channel modulators, and the parameters containing mRNA expression,  $I_{Kur}$ , effective refractory period (ERP) and action potential duration (APD) were utilized to reveal the improvement degree of AF. In principle the Kv1.5 modulators can lengthen the time course of ERP and APD to protect heart from the harm of AF.

Although the structure of Kv1.5 protein has not been characterized yet, current researches can provide information for the development of Kv1.5 inhibitor according to Fragment-Based Drug Design and Structure-Based Drug Design. In regard to the design of Kv1.5 inhibitor, for the instance of the typical candidate vernakalant, in the pharmacophore model, both hydrogen bond receptor, hydrogen bond donor and hydrophobic groups should be present in the structure (Figure 2A) to paly a role in transmembrane effect to interact with the Kv1.5 channel. From the potential binding domain of vernakalant in Kv1.5[8, 14] (Figure 2B), we can see that the positively charged moiety bound in the cationophilic inner pore (mainly formed by electron-donating residues including alanine, leucine and valine) to form the a cationic "blocking particle" causing the block of potassium channel, additionally, the uncharged dimethoxyphenyl moiety of a vernakalant have a tendency to bind in hydrophobic subunit interfaces including residues Ile 502 and Val 505. Functionally important residue isoleucine I502 in the inner helix S6 is exposed into the subunit interface of the pore module rather than into the inner pore. It is worth noting that mutations of Ile 502 decrease potency of vernakalant, flecainide and AVE0118, which are the ligands with long hydrophobic tail in the side chain of structure.

It seems that the introduction of heterocyclic rings including pyrrole (vernakalant, bepridil, clemizole and BMS-394136) and piperdine (lobeline, CD-160130, bupivacaine, paroxetine and donepezil ) is important because these moieties usually influence the acidifcation conditions of the molecules, which potentially protonated and thus positively charged drug may enter deeply into the channel pore in a voltage-dependent way [15].



**Figure 2.(A)** Pharmacophore model of vernakalant (cyan ball: hydrophobic center; yellow ball: aromatic center; green ball: hydrogen bond receptor; pink ball: hydrogen bond donor; red ball: ionizable positive ceter); (**B**) potential binding domain of vernakalant in Kv1.5 (H-bond is expressed as green dashed).

Because of the definite curative effects and pharmacokinetic parameters proved by clinical trials, conventional drugs in new use trends to be a feasible way to develop new therapy. Multiple cardiovascular drugs not designed for targeting Kv1.5 have shown Kv1.5 inhibitory effect including quinidine (**9**) and diltiazem (**10**), however, theselectivity of these compounds on Kv1.5 is still needed to investigate.

As for other clinical drugs, CNS agents including donepezil (15), which is generally used as anti-Alzheimer's agent, paroxetine (16), fluoxetine (17) and sertraline (18), which are usually used as antidepressant agent, bupivacaine (23), propofol (24), midazolam (25), tolbutamide (26) and benzocaine (27), which are utilized as anesthetic agents in common. *h*ERGs (human Ether-à-go-go-Related Gene) are widely associated with CNS diseases [16-18], thus it is not strange that active CNS agents can effectively modulate Kv1.5 according to the homology of the protein. Especially the neurotransmitter acetylcholine, which is an important substance that modulates the acetylcholine-activated K<sup>+</sup> current [19], however, only

the piperidine type acetylcholine inhibitor donepezil showed significant inhibitory effect on Kv1.5, the same phenomenon was not present in another inhibitor tacrine [15], suggesting the selectivity of the binding site of Kv1.5.

Generally, Kv1.5 drugs in development are not going smoothly. The projects listed in the Table 1 have been discontinued till now. Effectiveness, toxicity and druggability should be taken into account at this stage.Persistence of investigation in this field is necessary because the listed compound like AZD-7009 (30) can not only alleviate the suffering of patients from intermittent AF but also play roles in relieving durative AF which continues attack more than 48 hours [20]. The major voltage-gated K<sup>+</sup> channels expressed in the vasculature are Kv1.2, Kv1.5, Kv2.1, and Kv7.4/7.5[21].Kv1.3, another Shaker-related family Voltage-gated K+ channel, is closely related to the hERG channels regulated byKv11.1 [22], which are the important targets influencingprolong QT syndrome and torsade de pointes attributed to the gain-of-function mutationsbeing requested details of clinical candidates by drug regulatory authorities.Limitations in the ability of high-throughput screening methods to monitor the complex behavior of hERG has restricted the discovery of activators. It is noteworthy that some inhibitors of Kv1.5 channels listed in Table 1 are not specific Voltage-gated K+ channelfor Kv1.5, some of which also block Kv1.3 channels: e.g. 4-aminopiridine (2), nifedipine (6), diltiazem (10), tetraethylammonium (11), propofol (24) [23], resveratrol (52) [24] and correolide (55). Application of these drugs may result in side-effects related to the inhibition of Kv1.3 channels like immunosuppression, thus toxicity to hERG-related targets of Kv1.5 developing candidates should be paid more attentions. Additionally, in the field of immunization[25], nuclear factor erythroid 2-related factor (Nrf2)-induced oxidative stress-inducible protein sequestosome1/p62 enhances he inhibition of pulmonary arterial Kv1.5 channels under acute hypoxia, and sequestosome1/p62-Kv1.3-integrin axis provides novel insight into the molecular mechanisms underlying redox-regulated cell signaling

in stress-induced biological response, which broaden the potential direction in the future.

A variety of natural products have been proved to modulate Kv1.5, the exploration of novel skeleton could be helpful to the current dilemma. Among the isolated compounds, terpenoids (38-41), alakaloids (42-47) and flavonoids (48-50) are the main types. Terpenoids are widely reported to inhibit potassium channels [26-28], however, the stability and difficulty in preparation because of the lack of fluorescence group and the abundant in chiral carbon are worth worrying in the development. Alakaloids, as well as polypeptides like kaliotoxin (54) and marine drugs like tetrodotoxin, have been disclosed to exhibit ion channel activity, but the toxicity of this type of compounds is also needed to concern, after all, hERG toxicity has attached the attention of FDA and drugs like bepridil has been withdrawn because of the toxicity [29]. More preparation and modification works are waiting for possessing. Bioactive flavonoids are also proved to modulate Kv1.5 channel, among them quercetin (50) is a minor compound to be activator of Kv1.5, with the tendency of developing flavonoids and phenols as health care products or food additives, this class of compounds may play a role in prevent against Kv1.5 disease daily.

#### Synthetic Kv1.5 inhibitors and SAR investigations

In this part, we collated the information about chemical synthesis, pharmacological properties and SAR investigations in the published literatures ranging from 2003 to 2019 and summarized them with a timeline clue. The previous work was briefly introduced in the description about the potential synthetic derivatives and chemical structure of compounds and the SAR studies were listed in the corresponding figures in the perspective of medicinal chemistry. As we can see, multiple scaffolds including 5-methoxypsoralen (60and 68), tetrahydroindolone (62-65), benzopyran sulfonamides (70-72), dihydropyrazolopyrimidine (73 and 81)

# and phenylquinazoline(90-92).

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#### Table 1. Active KV 1.5 modulators.

No	Name	CAS	Status	Model	Mechanism	Ref.
			Clinical	cardiovascular drugs	3	
1		54-96-6	Approved	Smooth muscle cells	Blocking <i>h</i> Kv1.5 current with a threshold fur activation near -45 mV.	[30]
2	4-Aminopyridine	504-24-5	Approved	HEK cells	Inhibiting $h$ Kv1.5 current after long-term treatment, abbreviating the prolongation of action potential duration in chronic AF.	[31]
3		794466-70-9	Approved, investigation al	HEK cells	Selective blocking Kv1.5 channel by interacting with important residues including Thr 479, Thr 480, Ile 502, Val 505, and Val 508	[32]
4	Vernakalant	1951-25-3	Approved, investigation al	Papillary muscles or single ventricular cells	Decreasing the amount of mRNA for Kv1.5.	[33]
5	$F_{3}C$ $CF_{3}$ $HN$ $HN$ $F_{3}C$ $O$ $NH$ $F_{3}C$ $O$ $Flecainide$	54143-55-4	Approved, withdrawn	Xenopus laevis oocytes	Producing open-channel block of Kv1.5 with sensitively interacting with key residues including Asp 469, Val 481 and Ile 502 in the S6 region of Kv1.5.	[34]

No	Name	CAS	Status	Model	Mechanism	Ref.
6		21829-25-4	Approved	HEK cells	Blocking <i>h</i> Kv1.5 channels with K₄of 6.3 µM, affected by mutations like Arg 487 similar to those known to affect outer pore C-type inactivation.	[35]
7	Nifedipine O O N H H Propafenone	54063-53-5	Approved	Ltk <sup>-</sup> cells	Inhibiting <i>h</i> Kv1.5 current with Kavalue of 9.2 μM, showing time-dependent and dose-dependent manners simultaneously.	[36]
8	O OH 5-Hydroxy-propafenone	86384-10-3	-	Ltk <sup>-</sup> cells	Inhibiting <i>h</i> Kv1.5 current with K <sub>d</sub> value of 4.4 μM, showing time-dependent and dose-dependent manners simultaneously.	[36]
9	HO <sub>M</sub> , Quinidine	56-54-2	Approved, investigation al	HEK cells	Producing a voltage-dependent block between +30 and +120 mV (Kd at +60 mV = 7.2 μM) with an equivalent electrical distance in the steady state.	[37]
10	Diltiazem	42399-41-7	Approved, investigation al	CHO cells	Blocking <i>h</i> Kv1.5 channels, in a frequency-dependent manner exhibiting a biphasic dose-response curve (IC50: 4.8 nM and 42.3 μM) by binding to the open and the inactivated state of the channels.	[38]

No	Name	CAS	Status	Model	Mechanism	Ref.
11	Tetraethylammonium	66-40-0	Experimental , investigation al	BT-474 breast cancer cell	Blocking $h$ Kv1.5 channels in a delayed rectifier manner	[39]
12	CI-CI-CI-CI-CI-CI-CI-CI-CI-CI-CI-CI-CI-C	68379-03-3	-	CHO cells	Inhibiting <i>h</i> Kv1.5 current with concentration-dependent acceleration of the apparent channel inactivation in both outside-out and inside-out patches.	[40]
13	N Chromanol 293B	163163-23-3	-	CHO cells	Blocking hKv1.5 current stereoselectively, the results showed that (-)-[3R, 4S] was more potent than the (-)-enantiomer.	[41]
14	Bopridil	64706-54-3	Approved, withdrawn	HEK cells	Inhibiting the <i>h</i> Kv1.5 channel current with the IC <sub>50</sub> value of 6.6 $\mu$ M.	[42]
			Othe	r clinical drugs		
15	o Donepezil	120014-06-4	Approved	HEK cells	Resulting in a rapid and reversible block of Kv1.5 currents (IC50: 72.5µM) with a significant delay in the duration of activation and deactivation, and the outer mouth region was proved to be the target site.	[15]

No ·	Name	CAS	Status	Model	Mechanism	Ref.
16		61869-08-7	Approved, investigatio nal	CHO cells	Slowing the deactivation time course, resulting in a tail crossover phenomenon when the tail currents, recorded in the presence and absence of paroxetine, were superimposed.	[43]
17	HN CF <sub>3</sub>	54910-89-3	Approved, vet approved	Human PASMCs	Protecting against big endothelin-1 induced anti-apoptosis and rescued Kv1.5 channels in human pulmonary arterial smooth muscle cells.	[44]
18		79617-96-2	Approved	CHO cells	Reducing Kv1.5 whole-cell currents in a reversible dose-dependent manner and accelerated the decay rate of inactivation of Kv1.5 currents without modifying the kinetics of current activation.	[45]
19	Cortisone	53-06-5	Approved	Xenopus oocytes	Suppressing the amplitude of Kv1.5 channel current with IC50 value of 50.2 $\mu$ M.	[46]
20	HO HO HO H H H H H H H H H H H H H H H	50-23-7	Approved, vet approved	Xenopus oocytes	Suppressing the amplitude of Kv1.5 channel current with IC50 value of 33.4 μM.	[46]

No	Name	CAS	Status	Model	Mechanism	Ref.
21	Spiropolactono	52-01-7	Approved	Male Wistar rats	Shorting the APD <sub>90</sub> and increasing the expression of Kv1.5.	[47]
22	$F_3^C \xrightarrow{N}_{N-1} \xrightarrow{O}_{NH_2}^{O}$ Celecoxib	169590-42-5	Approved, investigatio nal	Ltk <sup>-</sup> cells	Blocking <i>h</i> Kv1.5 channels with an IC <sub>50</sub> of 26.2 $\mu$ M for the peak current and 5.5 $\mu$ M for the current at the end of a 250 ms pulse to +60 mV.	[48]
23		38396-39-3	Approved, investigatio nal	Ltk- cells	Blocking the open of <i>h</i> Kv1.5 channels stereoselectively, the results showed the K <sub>d</sub> value for <i>R</i> (+)-enantiomer (4.1 $\mu$ M) 6-fold more potent than the <i>S</i> (-)-enantiomer (27.3 $\mu$ M).	[49 <i>,</i> 50]
24	Propofol	2078-54-8	Approved, investigatio nal, vet approved	CHO cells	Inducing a time-dependent decline of the $h$ Kv1.5 current (IC <sub>50</sub> : 62.9 $\mu$ M) during depolarizing steps and slowed the time course of tail current decay upon repolarization.	[4]
25	N N CI Midazolam	59467-70-8	Approved	HEK cells	Inhibited Kv1.5 current (IC50: 17 μM) without influence on the half-maximal activation voltage of Kv1.5 channels.	[51]

No	Name	CAS	Status	Model	Mechanism	Ref.
26	N N S Tolbutamide	64-77-7	Approved, Investigatio nal	insulin-secreting INS-1 cells	Activating Kv1.5 channel and the activation of secretion can be counteracted by an excessive stimulation of Kv channels in INS-1 cells which shortened the Ca <sup>2+</sup> signal and confines insulin secretion.	[52]
27	H <sub>2</sub> N O Benzocaine	94-09-7	Approved	Ltk <sup>-</sup> cells	Blocking <i>h</i> Kv1.5 channels in a voltage-dependent manner and modified the voltage-dependence of channel activation	[53]
			Drug	s in development		
28	$ \begin{array}{c}                                     $	1163-36-6	Phase 2 Clinical	HEK cells	Decreasing $I_{Ks}$ and human Kv1.5 channel current at doses of 3 and 10 $\mu$ M at voltages ranging from -14.3 to +34.7 mV.	[54]
29	AVE-1231	767334-89-4	Phase 1 discontinue d	CHO cells	Inhibiting <i>h</i> Kv1.5 current with IC <sub>50</sub> value of 3.6 μM, blocked early atrial K <sup>+</sup> channels and prolonged atrial refractoriness with no effects on electrocardiography intervals and ventricular repolarization.	[55]
30	AZD-7009	864368-79-6	Phase 2 discontinue d	CHO cells	Blocking <i>h</i> Kv1.5 current with IC <sup>50</sup> value of 27 $\mu$ M with a slight decrease at higher frequency.	[56]

No ·	Name	CAS	Status	Model	Mechanism	Ref.
31	$ \begin{array}{c} F \\ C \\ O \\ N \\ H \\ BMS-394136 \end{array} $	343246-73-1	Phase 1 discontinue d	Mouse fibroblast L929 cells	Showing excellent activity in blocking Kv1.5 (IC50: 0.05 μM) and very good selectivity over <i>h</i> ERG, sodium and L-type calcium ion channels.	[57]
32	HN N BMS-919373	1272353-82-8	Phase 1 Discontinu ed	Mammalian L-929 cells	Blocking <i>h</i> Kv1.5 current with IC50 value of 0.05 μM with an acceptable <i>in vitro</i> selectivity and liability profile and a good pharmacokinetic profile across species.	[58]
33	MK-0448	875562-81-5	Phase 1 discontinue d	HK2BN9 cells	Blocking Kv1.5 current in an expression system and concentration-dependently elevated the plateau phase of atrial action potentials (APs).	[59]
34	XEN-D0103 (Undisclosed structure)	1410180-16-3	Phase 2 discontinue d	CHO cells	Prolongating action potential duration (APD) and suppressed APs at high stimulation rates in sinus rhythm (SR), paroxysmal AF ( <i>p</i> AF) tissue.	[60]
35	LY294002	154447-36-6	Experiment al	CHO cells	Acting directly on <i>h</i> Kv1.5 currents as an open channel blocker with key interacting residues located in the pore region (Thr 480, Arg 487) and the S6 segment (Ile 502, Ile 508, Leu 510, Val 516).	[9]

No	Name	CAS	Status	Model	Mechanism	Ref.
36	HO HO SSR149744C	752253-75-1	-	CHO cells	Inhibiting several potassium currents including $I_{\text{Kr}}$ , $I_{\text{Ks}}$ , $I_{\text{K(ACh)}}$ and $I_{\text{Kv1.5}}$ at the doses of 0.01-30 $\mu$ M.	[61]
37		1034194-07-4	-	HEK cells	Inhibiting <i>h</i> Kv1.5 current slightly when specially blocked the Kv11.1 channel.	[62]
	CD-160130 Natural products		Type			
38	HOW O D HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O H HOW O HOW HOW	2334247-91-3	Terpenoid	CHO cells	Blocking Kv1.5 with an IC50 value of 6.94 $\mu M.$	[63]
39	HO I I I I I I I I I I I I I	2334247-94-6	Terpenoid	CHO cells	Blocking Kv1.5 with an IC50 value of 0.30 $\mu M.$	[63]

No	Name	CAS	Status	Model	Mechanism	Ref.
40		57444-62-9	Terpenoid	C6 glioma cells	Inhibiting the <i>h</i> Kv1.5 current in time and dose-dependent manners	[64]
	Resiniferatoxin O					
41		13018-10-5	Terpenoid	Ltk <sup>-</sup> cells	Inhibiting the $h$ Kv1.5 current in time and voltage-dependent manners, with an IC <sub>50</sub> value of 2.51 $\mu$ M at +60 mV, accelerated the inactivation kinetics of the $h$ Kv1.5 channel, and slowed the deactivation kinetics of the $h$ Kv1.5 current, resulting in a tail crossover phenomenon.	[65]
42		1394-48-5	Alkaloid	guinea pigs	Blocking <i>I</i> -Kv1.5 slight with the ratio of 20.6% at the dosage of 200 μM.	[66]
43	Guanfu base A	90-69-7	Alkaloid	HEK cells	Accelerating the decay rate of Kv1.5 inactivation, decreasing the current amplitude at the end of the pulse in a concentration-dependent manner with a IC <sub>50</sub> value of 15.1 $\mu$ M.	[67]

No	Name	CAS	Status	Model	Mechanism	Ref.
44		4360-12-7	Alkaloid	Xenopus oocytes	Inhibiting Kv1.5 with an IC50 of 1.70 μM in <i>Xenopus</i> <i>expression</i> system, resulting in a mild leftward shift of Kv1.5 activation curve.	[68]
45	Ajmaine O Papaverine	58-74-2	Alkaloid	Ltk-cells	Blocking <i>h</i> Kv1.5 channels and native <i>h</i> Kv1.5 channels in a concentration-, voltage-, state-, and time-dependent manner.	[69]
46	H H V N Tetrahydropalmatine	2934-97-6	Alkaloid	HEK cells	Blocking Kv1.5 currents dose-dependently with an IC <sub>50</sub> value of 53.2 $\mu$ M, inhibited the delayed rectifier effect of Kv1.5 resulting in a potential left shift of the inactivation curve.	[70]
47	HO HO HO HO HO HO HO HO HO HO HO HO HO H	302-27-2	Alkaloid	Xenopus laevis oocytes	Producing a voltage-, time-, and frequency-dependent inhibition of Kv1.5 (IC50: 0.796 μM).	[71]

No	Name	CAS	Status	Model	Mechanism	Ref.
48		529-44-2	Flavonoid	HEK cells	Inhibiting <i>I</i> <sub>kur</sub> and the expression of <i>h</i> Kv1.5 in a dose-, time- and frequency-dependent manner.	[72]
49	Myricetin O U Trimethylapigenin	5631-70-9	Flavonoid	HEK cells	Suppressing <i>h</i> Kv1.5 current in HEK 293 cell line (IC50: 6.4 μM)and the ultra-rapid delayed rectify K <sup>+</sup> current <i>I</i> <sub>Kur</sub> in human atrial myocytes (IC50: 8.0 μM) by binding to the open channels and showed a use- and frequency-dependent manner.	[73]
50		117-39-5	Flavonoid	Xenopus laevisoocytes	Activating <i>h</i> Kv1.5 channels (EC <sub>50</sub> : 37.8 $\mu$ M) by interacting with key residue Ile 502 in S6 region.	[74]
51	HO O O O O O O O O O O O O O O O O O O	480-44-4	Flavonoid	HEK cells	Blocking open <i>h</i> Kv1.5 channels by binding to their S6 domain influenced by the interaction of V505A, I508A, and V512A.	[75]
52	но но Resveratrol	501-36-0	Phenol	Human PASMCs	Reducing the expression of Kv1.5 mRNA to reverse monocrotaline-induced pulmonary vascular and cardiac dysfunction.	[76]

No ·	Name	CAS	Status	Model	Mechanism	Ref.
53	Decursin	5928-25-6	Coumarin	Ltk⁻ cells	Inhibiting $h$ Kv1.5 current in a concentration- and use- dependent manner, with an IC <sub>50</sub> value of 2.7 $\mu$ M at +60 mV, accelerated the inactivation kinetics of the $h$ Kv1.5 channel, resulting in a tail crossover phenomenon.	[77]
54	Kaliotoxin	145199-73-1	Polypeptid e	T cell	Inhibiting $h$ Kv1.5 current in a dose dependent manner.	[64]
55		190017-00-6	Nor-triterp enoid	CHO cells	Inhibiting Kv1.5 with an IC50 of 1.77 μM and influenced by the mutations T480A, V505A, I508A, as well as V516A.	[78]
56	Correolide $O_{S} OH^{NH_2}$ $O^{Taurine}$	107-35-7	Amino acid	Male Wistar rats	Down-regulating the mRNA expression level of Kv1.5.	[79]

(86-88) have been reported to be effective in inhibiting Kv1.5, suggesting potential directions for the investigation about the Kv1.5 inhibitors in the future. It is noteworthy that researches from Bristol-Myers Squibb paid great efforts in this field with a lot of data about pharmacology and pharmacokinetics of active compounds in blocking Kv1.5, increasing the possibility that we human beings conquer the diseases targeting Kv1.5.



7 8

Figure 3.SAR of biphenyl derivatives.

9 In 2003, Peukert and co-workers [80] synthesized a series of ortho, 10 ortho-disubstituted bisaryl compounds as blockers of the Kv1.5 channel. Among 11 the derivatives, the most potent compounds  $57(IC_{50}: 0.7 \mu M)$  and  $58(IC_{50}: 0.16 \mu M)$ inhibited the Kv1.5 channel with sub-micromolar half-blocking concentrations 13 and displayed 3-fold selectivity over Kv1.3 and no significant effect on the HERG 14 channel and sodium currents (Figure3).



15 16

Figure 4.SAR of anthranilic amides.

In 2004, Peukert et al. [81] synthesized several anthranilic amides as novel blockers of the Kv1.5 channel. The most hopeful analogue **59** showed moderate Kv1.5 inhibition (IC<sub>50</sub>: 0.7  $\mu$ M) with good oral bioavailability, however, no significant effect on the *I*<sub>Kr</sub> current of **59**was detected (**Figure4**).



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Figure 5.SAR of phenoxyalkoxypsoralen analogues.

23 Inspired from the precursor 5-methoxypsoralen isolated from *Rutagraveolens*, 24 Schmitz and colleagues [82] prepared a series of phenoxyalkoxypsoralen analogues 25 and evaluated their voltage-gated ion channel blocker potency. The most potent 26 and "druglike" compound of this series, 5-(4-phenoxybutoxy) psoralen (PAP-1, 60), 27 blocks Kv1.3 in a use-dependent manner, with a Hill coefficient of 2 and an EC<sub>50</sub> of 28 2 nM, by preferentially binding to the C-type inactivated state of the channel. 29 PAP-1 is 23-fold selective over Kv1.5, 33- to 125-fold selective over other Kv1 30 family channels, and 500- to 7500-fold selective over Kv2.1, Kv3.1, Kv3.2, Kv4.2, 31 HERG, calcium-activated K channels, Na, Ca and Cl channels. PAP-1 does not 32 exhibit cytotoxic or phototoxic effects, is negative in the Ames test, and affects 33 cytochrome P450-dependent enzymes only at micromolar concentrations (Figure 34 5).



**Activity:** 4-position of substitutions are favoured and lipophilicity is well tolerated, but the difference between EDGs and EWGs is not substantial.

35

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Figure 6.SAR of (2-phenethyl-2H-1,2,3-triazol-4-yl)(phenyl) methanones.

37 2006, Blass In al. [83] cluster of et synthesized а (2-phenethyl-2H-1,2,3-triazol-4-yl) (phenyl) methanones and examined for utility 38 39 as Kv1.5 channel blockers for the treatment of atrial fibrillation. The results showed 40 that O substitution in the 4-position of the acetophenone-derived portion of the

- 41 scaffold is highly favored, and the most active compound 61blockaded Kv1.5 for
- 42 99% at the concentration of  $1 \mu M$ (**Figure 6**).



Figure 7.SAR of tetrahydroindolone-derived carbamates.

Fluxe and co-workers [84] synthesized multiple tetrahydroindolone-derived carbamates as the potent Kv1.5 blockers. The most promising analogues **62** and **63**exhibited strongest Kv1.5 inhibitory effect with IC<sub>50</sub> values of 67 and 21 nM, respectively. They were also very selective over *h*ERG (>450 fold) and L-type calcium channels (> 450 fold) (**Figure7**).



50 51

Figure 8.SAR of tetrahydroindolonederived semicarbazones.

52 Subsequently, Wu et al. [85] designed and synthesized tetrahydroindolone 53 derived semicarbazones as selective Kv1.5 blockers. Compounds **64** and **65**showed 54 good selectivity for blockade of Kv1.5 (IC<sub>50</sub>: 0.13 μM for two compounds), 55 moreover, in an anesthetized pig model, compounds **64** and **65**increased atrial ERP 56 about 28%, 18%, respectively, in the right atrium without affecting ventricular ERP 57 (**Figure8**).



Figure 9.SAR of diisopropyl amide derivaitives.

Based on a diisopropyl amide scaffold, a series of potent Kv1.5 ion channel antagonists were synthesized by Nanda and colleagues [86]. The most active derivative **66**, which was a single active enantiomer of the diastereomerically pure racemic analog, exhibited significant atrial-selective effects in an *in vivo* model (IC<sub>50</sub>: 150 nM) (**Figure 9**).



65 66

67 Trotter and co-workers [87] design and synthesized group а of isoquinoline-3-nitriles as orally Kv1.5 antagonists for the treatment of AF. The 68 69 ethanolamide derivative67exhibited improved potency (Kv1.5 HT-Clamp IC50: 60 70 nM), excellent selectivity versus hERG, and good pharmacokinetic properties. Rat 71 EP experiments confirmed that the compound potently increased ARP without 72 significant effects on AVRP (Figure 10).



Figure 11.SAR of psoralen derivatives.

73 74

Figure 10.SAR of isoquinoline-3-nitriles.

In 2007, Eun et al. [88] synthesized multiple psoralen derivatives as hKvl.5 channel blocker. Among them, compound**68** was the most potent in blocking hKvl.5 (IC<sub>50</sub>: 27.4 nM), much stronger than the lead compound psoralen. Compound **68**accelerated the inactivation kinetics of the hKvl.5 channel, slowed the deactivation kinetics of hKvl.5 current resulting in a tail crossover phenomenon. Compound **68**inhibited hKvl.5 current in a use-dependent manner (**Figure 11**).



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Figure 12.SAR of thiazolidine derivatives.

Jackson and co-workers [89] prepared several classes of thiazolidine-based Kv1.5 blockers. The most promising analogue**69** derived from 3,4-dimethylacetophenone exhibited the strongest inhibitory effect with an IC<sub>50</sub> value of 69 nM(**Figure 12**).



Figure 13.SAR of benzopyran sulfonamides.

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Lloyd et al. [90] synthesized a series of benzopyran sulfonamides and determined Kv1.5 potassium channel blocking effects. Among the productions, derivative **70**exhibited the most significant activity (IC<sub>50</sub>: 57 nM), and the moderate inhibition (35%) of *h*ERG at the concentration of 10  $\mu$ M (**Figure 13**).



Figure 14.SAR of thiazolidine derivatives.

In 2008, the benzopyran sulfonamides derivatives were further investigated [91]. Compound **71**and **72**were considered as the most active derivatives in the two series of compounds with IC<sub>50</sub> values for 46 and 378 nM in the inhibition of current in L-929 cells model, respectively. Additionally, at the concentration of 1  $\mu$ M, compound **72**displayed the most significant inhibitory effect in current in L-929 cells with the inhibitory ratio for 89% (**Figure 14**).



## 102 103

# Figure 15.SAR of dihydropyrazolopyrimidine derivatives.

104 Vaccaro and co-workers [90] synthesized a series of 105 dihydropyrazolopyrimidine analogues as Kv1.5 inhibitor. The most promising 106 compound **73**showed the best potential in of suppressing Kv1.5, with inhibitory 107 effects on HERG (69%) and  $I_{Na^{10}}$  (42%) at the concentration of 10 µM (**Figure 15**).





Figure 16.SAR of aryl sulfonamido tetralin derivatives.

In 2008, Gross and co-workers [92] synthesized aryl sulfonamido tetralin asKv1.5 inhibitor according to the basis of previous work. Among the productions,

112 compound 74exhibited remarkable Kv1.5 inhibition with IC<sub>50</sub> value for 90 nM, in 113 addition, moderate hERG inhibition was detected at the dose of 10  $\mu$ M (39%),

114 indicating the potential of further development of clinical candidates (**Figure 16**).



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Figure 17. SAR of imidazolidinone derivatives.

117 According to the structure of marketed drugs amiodarone and vernakalant, 118 Blass et al. [93] synthesized a series of imidazolidinone derivatives as a potential 119 treatment for atrial arrhythmia. KVI-020/WYE-160020 (75) exhibited the efficacy in 120 clinically relevant models of AF and mechanistic models of the cardiac action 121 potential with acceptable pharmacokinetic and pharmaceutical properties. The 122 pharmacology IC50 values for compound 75 in Kv1.5, hERG, Nav1.5, Cav1.3, 123 Cav1.2, Kv1.1, Kv1.3 and Kv4.3 for 0.48, 15.1, > 30, 23.4, > 30, 2.66, 1.41 and 3.87 μM 124 *invitro*, respectively (Figure 17).



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Figure 18. SAR of pyrazolodihydropyrimidines.

127 In 2010, Lloyd and co-workers [58] developed series of а 128 pyrazolodihydropyrimidines as potent and selective Kv1.5 blockers based on the 129 previous studies. The most promising analogue BMS-394136 (76) displayed 130 excellent activity in blocking Kv1.5 (IC50: 50 nM) and very good selectivity over hERG, sodium and L-type calcium ion channels with good pharmacokinetic 131 132 parameters (Figure 18).



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Figure 19. SAR of heteroarylsulfonamides.

In 2012, Benjamin Blass[94] prepared several heteroarylsulfonamides as Kv1.5 inhibitors. The active analogues **77**, **78**and **79** exhibited 100% inhibition of Kv1.5 using stably transfected HEK293 cells and the FLIPR potassium ion channel assay, suggesting a good potential for further investigation (**Figure 19**).



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Figure 20. SAR of dihydropyrazolo[1,5-a]pyrimidine derivatives.

Finlay and colleagues [95] prepared several dihydropyrazolo[1,5-a]pyrimidine derivatives. Among the synthetic compounds, **80**showed potential to be a selective  $I_{Kur}$ inhibitor with Kv1.5 IC<sub>50</sub> for 0.15 µM and *h*ERG for IC<sub>50</sub>> 10 µM. Furthermore, favorable pharmacokinetic properties in rats and dogsof 80were determined, **80**was identified with less than 1% GSH adduct formation with an improved PK profile and equivalent PD efficacy to the lead compound (**Figure 20**).



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#### Figure 21. SAR of trifluoromethylcyclohexyl triazole analogues.

In 2013, triazolo and imidazo were introduced into the active scaffold dihydropyrazolopyrimidine[96]. Trifluoromethylcyclohexyl triazole analogue **81**was identified as a potent and selective Kv1.5 inhibitor (IC<sub>50</sub>: 133 nM) with an acceptable PK and liability profile. Compound **81**demonstrated an improved rat PK profile and was advanced to the rat PD model (**Figure 21**).



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Figure 22. SAR of indole derivatives.

With the help of pharmacophore model, Guo et al. [97] designed and synthesized a series of indole derivatives as potent Kv1.5 inhibitors. The most promising compound **82**displayed significant  $I_{Na}$ , HEK 293 *h*Kv1.5 and CHO *h*ERG inhibitory activities with IC<sub>50</sub> values of 52.6, 0.51 and 418.35  $\mu$ M, respectively, which displayed remarkable selectivity and ameliorating effects on AERP and VERP (**Figure 22**).



162

163 **Figure 23.** SAR of diphenylphosphinic amides and diphenylphosphine oxides.

Olsson and co-workers [98] possessed design and pharmacological evaluation of multiple potential hits targeting on Kv1.5. The compound **83** performed best *in vitro* activity with Kv1.5 IC<sub>50</sub> of 0.08  $\mu$ M in diphenylphosphinic amide and diphenylphosphine oxide analogues (**Figure 23**). However, both *h*ERG and IKs active and of **83** were detected and was judged unsuitable for *in vivo* testing, 169 conversely, the derivative **84** was regarded as the hopeful compound for further 170 development with Kv1.5 IC<sub>50</sub>, IKs, C<sub>eu20</sub>, QT<sub>max</sub> change values for 1  $\mu$ M, >33%, 0.6 171  $\mu$ M, <10%, respectively.



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Figure 24. SAR of lactam sulfonamides.

174 In 2014, the subsequent study was updated [99], a series of lactam sulfonamide 175 derivatives were prepared and evaluated the Kv1.5 inhibitory potency. The most 176 promising candidate 85 inhibited Kv1.5 with an IC<sub>50</sub> value of 0.21 µM, and caused a 177 marked increase in the atrium ERP with a  $C_{eu20}$  of 0.35  $\mu$ M, which was at the same 178 order of magnitude as the IC<sub>50</sub> value from the human cellular assay. The human hERG channel was blocked by compound 85 with an IC50 value of 30 µM, 179 180 indicating a 140-fold margin of the *h*ERG and Kv1.5 *in vitro* values. No measurable 181 change was noted in the QT-interval in the rabbit experiments, which also 182 indicated a good margin to block of the hERG channel. The compound 85 was well 183 tolerated in rabbits with no signs of the CNS-like side effects observed for other 184 Kv1.5 blockers (Figure24).



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Figure 25. SAR of phenethylaminoheterocycles.

Johnson et al. [100] synthesized phenethylaminoheterocycles and assayed for inhibition of the Kv1.5 potassium ion channel as a potential approach to the treatment of atrial fibrillation. Combination of the indazole with a cyclohexane-based template gave the most promising derivative **86**(Kv1.5 IC<sub>50</sub>: 138 nM) which demonstrated significant prolongation of AERP in the rabbit

# 192 pharmacodynamic model(Figure 25).





Figure 27. SAR of isoindolinones.

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In 2016, Kajanus et al. [102] synthesized multiple isoindolinone compounds as Kv1.5 blockers. The most potent compounds **88**and **89**exhibited inhibitory effect with the IC<sub>50</sub> values of 0.4 and 0.7  $\mu$ M on Kv1.5, respectively. The above mentioned

two compounds were found to have desirable *in vivo* PK properties in mouse
model (Figure 27).



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Figure 28. SAR of phenylquinazoline derivatives.

Finlay and co-workers [103] explored phenylquinazoline derivatives as Kv1.5 inhibitors. 5-phenyl-N-(pyridin-2-ylmethyl)-2-(pyrimidin-5-yl)quinazolin-4-amine (90) was identified as a potent and ion channel selective inhibitor (Kv1.5 IC<sub>50</sub>: 90 nM, *h*ERG inhibition: 43% at 10  $\mu$ M) with robust efficacy in the pre-clinical rat ventricular effective refractory period (VERP) model and the rabbit atrial effective refractory period (AERP) model (**Figure 28**).



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Figure 29. SAR of phenylquinazoline sulfonamide derivatives.

Subsequently in 2017, Gunaga et al. [58]modified the structure of **91**with a series of analogues and evaluated the  $I_{Kur}$  inhibitory effect. 5-[5-phenyl-4-(pyridin-2-ylmethylamino)-quinazolin-2-yl]

221 pyridine-3-sulfonamide (92) was identified as the lead compound in this series 222 with good selectivity over hERG (Kv1.5 IC50: 50 nM, hERG IC50: 1.9 µM). 223 Compound 91exhibited robust effects in rabbit and canine pharmacodynamic 224 models and an acceptable cross-species pharmacokinetic profile which was then advanced as a clinical candidate. Further optimization of 91to mitigate 225 pH-dependent absorption resulted in identification of the corresponding 226 227 phosphoramide prodrug (92) with an improved solubility and pharmacokinetic 228 profile(Figure 29).



229



Figure 30. SAR of oroidin derivatives.

231 According to the skeleton of *Agelas* alkaloids clathrodin, oroidin and hymenidin,

Zidar and colleagues [104] synthesized multiple derivatives as inhibitors of the voltage-gated potassium channels. The most potent inhibitor was the (E)-N-(3-(2-amino-1H-imidazol-4-yl)allyl)-4,5-dichloro-1H-pyrrole-2-carboxamide (93) with IC<sub>50</sub> values between 1.4 and 6.1 mM against Kv1.3, Kv1.4, Kv1.5 and Kv1.6 channels (Kv1.5 IC<sub>50</sub>: 6.1  $\mu$ M) (Figure 30).



Figure 31. SAR of oroidin MK-1832.

239 Wolkenberg et al. [105] told the story of the development of prospective 240 candidate MK-1832 (94)(Figure 31). Based on the structure of MK-0448, a cluster 241 of derivatives were synthesized and tested the Kv1.5 inhibitory effect and in vivo 242 and in vitro toxicity. MK-1832 (94) was considered to be best derivative with 243 pharmacological parameters including Kv1.5, Ikur, Ikr(hERG) IC50 values for 29, 11, 128000 nM, resepectively, and pharmacokinetic parameters including dog in vivo 244 245 atrial refractory period EC10 for 14 nM and threshold change in ventricular 246 refractory period > 25  $\mu$ M.



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Figure 32. SAR of 1,2-bis(aryl)ethane-1,2-diamines.

In 2019, Kajanus and colleagues [106] prepared potassium channel blocking 1,2-bis(aryl)ethane-1,2-diamines active as antiarrhythmic agents. The most promising analogue **95**displayed significant nanomolar potency in blocking Kv1.5

- in human atrial myocytes (IC<sub>50</sub>: 1.7 μM, *I*<sub>Kur</sub> IC<sub>50</sub>: 60 nM) and based on the PD data,
- the estimated dose to man was 700 mg/day (**Figure 32**).



Figure 33. SAR of aplysiatoxin derivatives.

256 Recently, natural products with novel structural motif as Kv1.5 inhibitor also 257 field. the gain progress in this In sequence of the isolation of 258 compound debromoaply siatoxin A (38) and debromoaply siatoxin B (39) [63], Tang 259 and co-workers [14] identified other novel aplysiatoxin derivatives from the marine 260 cyanobacterium Lyngbya sp. Among them, compound oscillatoxin E (96) with the 261 hexane-tetrahydropyran of a spirobicyclic system skeleton exhibited the strongest 262 Kv1.5 inihibition (IC<sub>50</sub>: 0.79 μM) in the CHO cells at HP of -80 mV (Figure 33).

#### 263 Conclusion

264 Herein the target and the pharmacological properties with structural, 265 pharmacological and SAR information of Kv1.5 modulators have been discussed. 266 Detailed descriptions of pharmacology parameters and SAR studies provide an 267 actionable path forward for medicinal chemists to optimize the structure of Kv1.5 268 modulators. Further experiments should improve the PK and safety after the 269 effectiveness is proved. Design and development of potential and selective Kv1.5 270 modulators are important and challenging tasks. Based on the existing 271 pharmacophoric requirements and potential protein structure parsed in the future, 272 novel effective Kv1.5 modulators may be designed and prepared [107, 108]. 273 However, gaps exist in the scientific studies on Kv1.5 modulators: Firstly, the 274 selectivity of existing Kv1.5 modulators remain to investigate, and more specific modulators aiming at Kv1.5 channel are needed in the future. Secondly, from the point of application, the market of AF is relatively small, the sales condition of marked anti-AF agents is not satisfactory as a whole, thus more depth pharmacological investigations of roles that Kv1.5 paly are required in the future. Moreover, the definite structure of Kv1.5 protein is still vacant, difficulties and potential fallacy are still consisting in the design of modulators only estimating by the pocket of homologous models.

SAR investigation is crucial for the development of novel promising clinical candidates. It is anticipated that the information compiled in this review article not only updates researchers with the recent reported pharmacology and SAR of Kv1.5 modulators, but also motivates them to design and synthesize promising Kv1.5 modulators with improved medicinal properties.

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## 293 Conflict of interest

294 None of the authors have any conflict of interest to disclose.

# 295 Abbreviations

- 296 AF: atrial fibrillation;
- 297 BLAST: Basic Local Alignment Search Tool;

- 298 Ceu20: unbound steady-state plasma concentration;
- 299 CHO cells: Chinese Hamster Ovary cells;
- 300 CNS: Central nervous system;
- 301 EDGs: Electron donating groups;
- 302 EWGs: Electron withdrawing groups;
- 303 HEK cells: Human Embryonic Kidney 293 cells;
- 304 *h*ERG: human Ether-à-go-go-Related Gene;
- 305 *h*Kv1.5 channels: human Kv1.5 channels;
- 306 Human PASMCs: Human Pulmonary Arterial Smooth Muscle Cells;
- 307 *I*Kur cardiac ultra-rapid delayed-rectifier;
- 308 IC<sub>50</sub>:50% inhibitory concentration;
- 309 Ile: Isoleucine;
- 310 Nrf2: nuclear factor erythroid 2-related factor;
- 311 SAR: Structure-Activity Relationship;
- 312 Thr: Threonine;
- 313 Val: Valine;
- 314 VERP: ventricular effective refractory period.

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