# Challenges Faced with Small Molecular Modulators of Potassium Current Channel Isoform Kv1.5

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MDPI

*Review*

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

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

[a]*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;*

[b]*Sorbonne Université, InstitutParisien de ChimieMoléculaire, CNRS UMR 8232, 4 place Jussieu, 75005 Paris, France;*

[c] *Department of Medicinal Chemistry, School of Pharmaceutical Engineering and Life Science, Changzhou University, Changzhou 213164, Jiangsu, China;*

[d] *Laboratory for Medicinal Chemistry, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium;*

[e] *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.

- 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.

## Introduction

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 $K^+$ 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 $K^+$ 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.

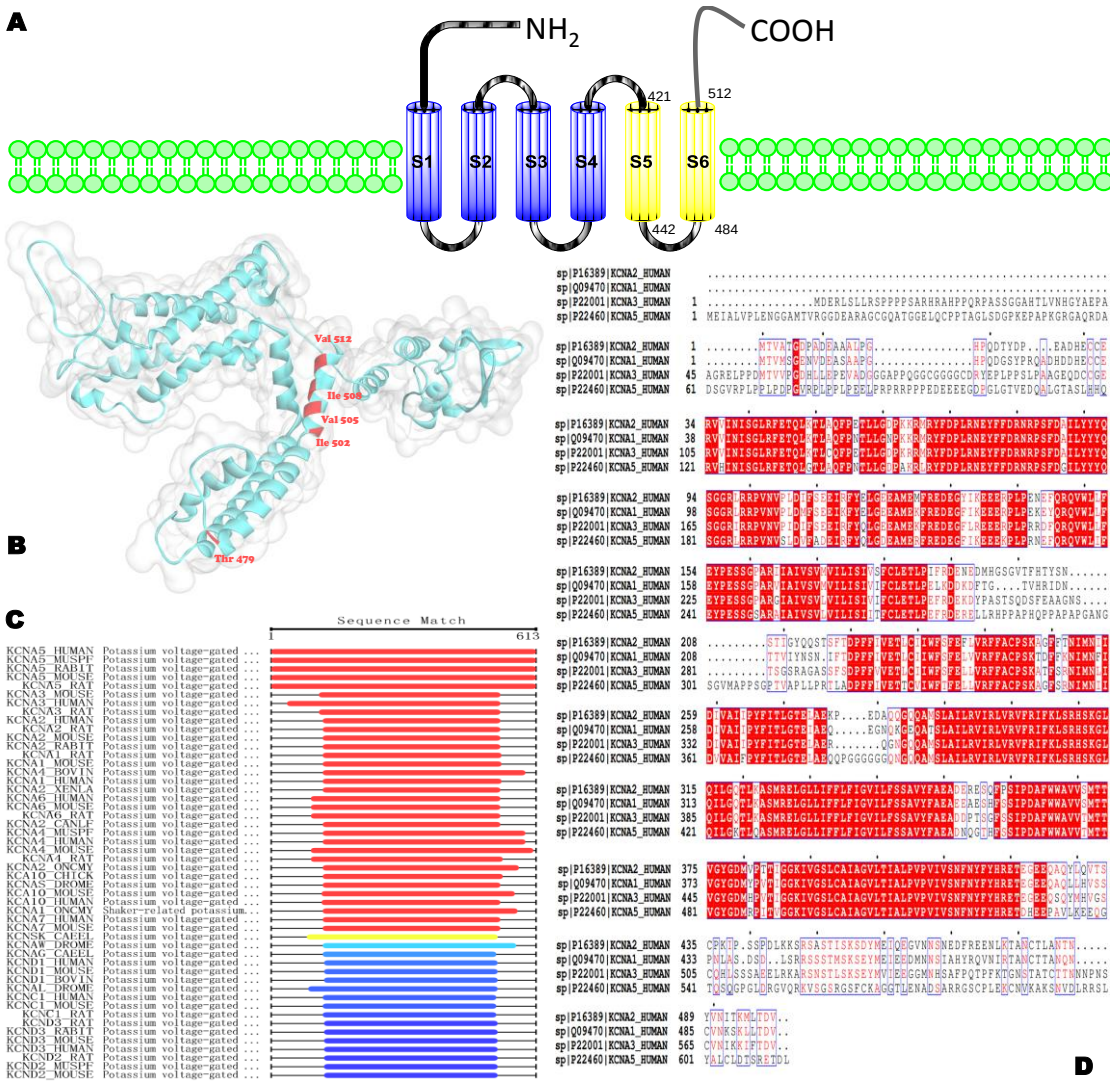



**Figure 1.** (**A**) Schematic representation of *h*Kv1.5 $\alpha$-subunit with the sequence of S6 region listed; (**B**) Homologous model of Kv1.5 (Q61672) with the range of 67.2% for sequence of Kv1.5 getting from the SWISS-MODEL database, some of the residues are slightly different with the contents 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 $Ltk^-$ 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].

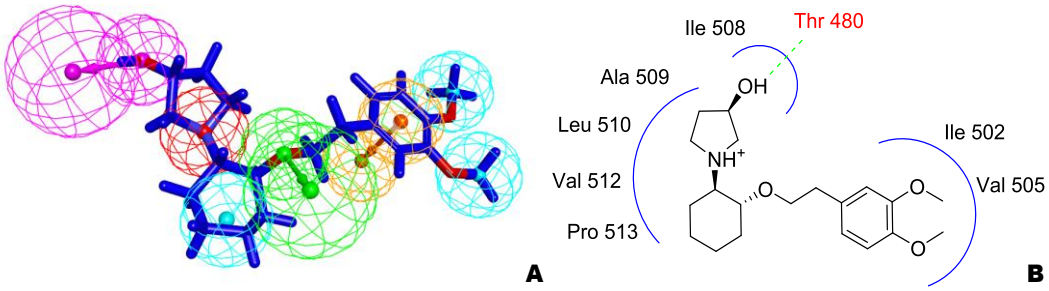



**Figure 2.**(**A**) Pharmacophore model of vernakalant (cyan ball: hydrophobic center; yellow ball: aromatic center; green ball: hydrogen bond receptor; pink ball: hydrogen bond donor; red ball: ionizable positive ceter); (**B**) potential binding domain of vernakalant in Kv1.5 (H-bond is expressed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

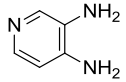
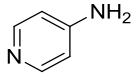
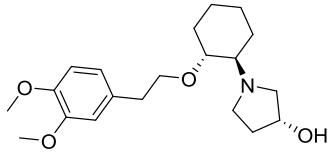
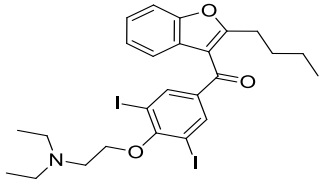
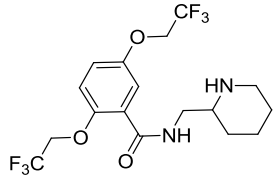
A variety of natural products have been proved to modulate Kv1.5, the exploration of novel skeleton could be helpful to the current dilemma. Among the isolated compounds, terpenoids (**38-41**), alakaloids (**42-47**) and flavonoids (**48-50**) are the main types. Terpenoids are widely reported to inhibit 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, *h*ERG 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.

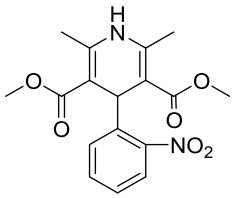
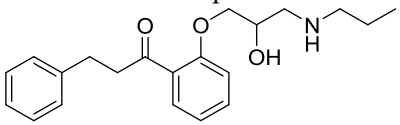
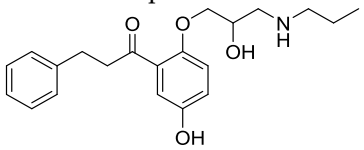
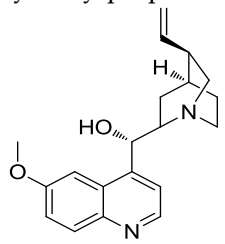
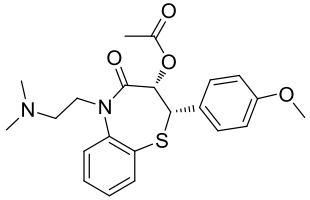
## Synthetic Kv1.5 inhibitors and SAR investigations

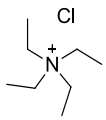
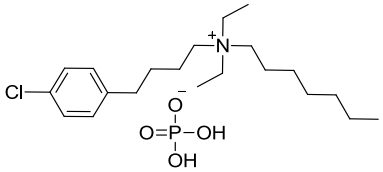
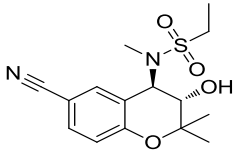
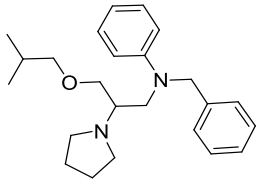
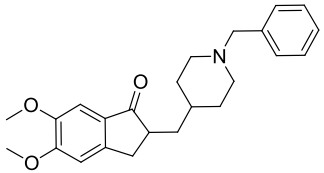
In this part, we collated the information about chemical synthesis, pharmacological properties and SAR investigations in the published literatures ranging from 2003 to 2019 and summarized them with a timeline clue. The previous work was briefly introduced in the description about the potential synthetic 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 (**60**and **68**), tetrahydroindolone (**62**-**65**), benzopyran sulfonamides (**70**-**72**), dihydropyrazolopyrimidine (**73** and**81**)

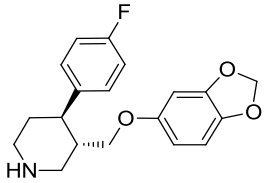
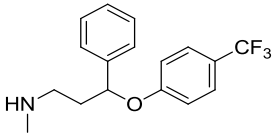
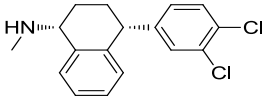
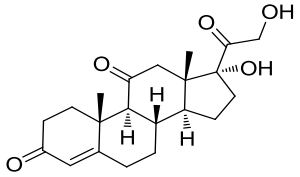
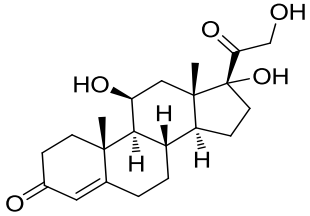
and phenylquinazoline(**90**-**92**).

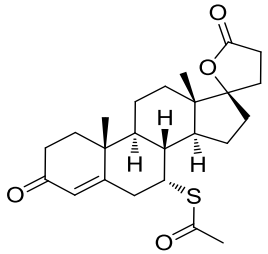
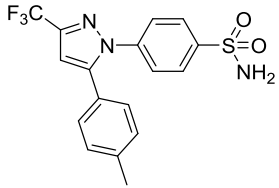
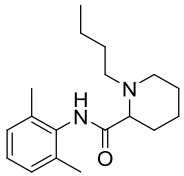
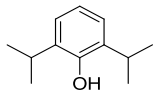
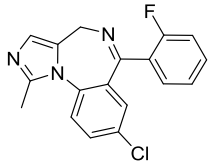
**Table 1.** Active KV 1.5 modulators.

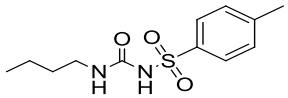
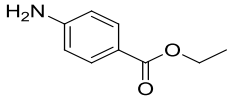
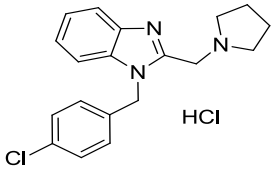
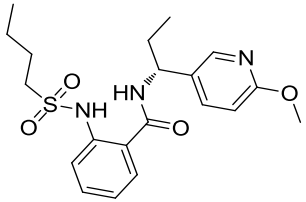
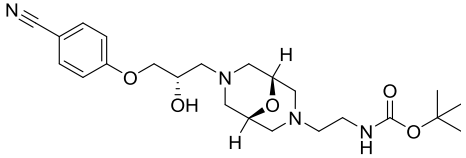
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| | | | ***Clinical cardiovascular drugs*** | | | |
| 1 |  3,4-Diaminopyridine | 54-96-6 | Approved | Smooth muscle cells | Blocking *h*Kv1.5 current with a threshold fur activation near -45 mV. | [30] |
| 2 |  4-Aminopyridine | 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 |  Vernakalant | 794466-70-9 | Approved, investigational | 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 |  Amiodarone | 1951-25-3 | Approved, investigational | Papillary muscles or single ventricular cells | Decreasing the amount of mRNA for Kv1.5. | [33] |
| 5 |  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] |

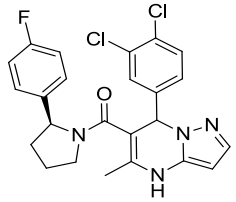
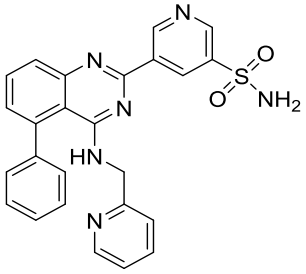
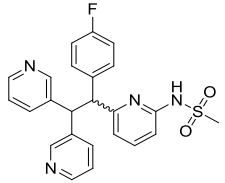
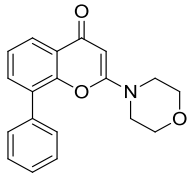
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 6 |  Nifedipine | 21829-25-4 | Approved | HEK cells | Blocking *h*Kv1.5 channels with $K_d$of 6.3 μM, affected by mutations like Arg 487 similar to those known to affect outer pore C-type inactivation. | [35] |
| 7 |  Propafenone | 54063-53-5 | Approved | Ltk- cells | Inhibiting *h*Kv1.5 current with $K_d$value of 9.2 μM, showing time-dependent and dose-dependent manners simultaneously. | [36] |
| 8 |  5-Hydroxy-propafenone | 86384-10-3 | - | Ltk- cells | Inhibiting *h*Kv1.5 current with $K_d$value of 4.4 μM, showing time-dependent and dose-dependent manners simultaneously. | [36] |
| 9 |  Quinidine | 56-54-2 | Approved, investigational | HEK cells | Producing a voltage-dependent block between +30 and +120 mV ($K_d$ at +60 mV = 7.2 μM) with an equivalent electrical distance in the steady state. | [37] |
| 10 |  Diltiazem | 42399-41-7 | Approved, investigational | CHO cells | Blocking *h*Kv1.5 channels, in a frequency-dependent manner exhibiting a biphasic dose-response curve ($IC_{50}$: 4.8 nM and 42.3 μM) by binding to the open and the inactivated state of the channels. | [38] |

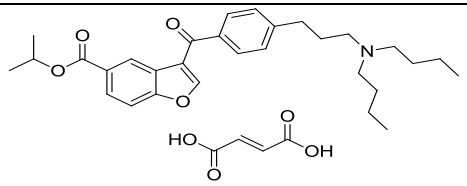
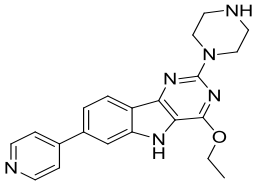
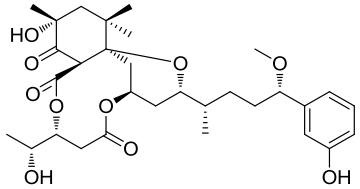
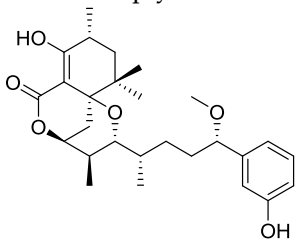
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 11 |  Tetraethylammonium | 66-40-0 | Experimental, investigational | BT-474 breast cancer cell | Blocking *h*Kv1.5 channels in a delayed rectifier manner | [39] |
| 12 |  Clofilium | 68379-03-3 | - | CHO cells | Inhibiting *h*Kv1.5 current with concentration-dependent acceleration of the apparent channel inactivation in both outside-out and inside-out patches. | [40] |
| 13 |  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 |  Bepridil | 64706-54-3 | Approved, withdrawn | HEK cells | Inhibiting the *h*Kv1.5 channel current with the $IC_{50}$ value of 6.6 μM. | [42] |
| | | | ***Other clinical drugs*** | | | |
| 15 |  Donepezil | 120014-06-4 | Approved | HEK cells | Resulting in a rapid and reversible block of Kv1.5 currents ($IC_{50}$: 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] |

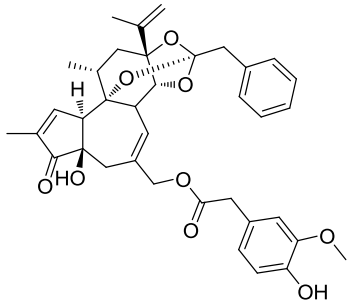
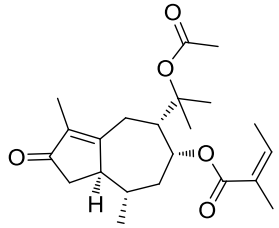
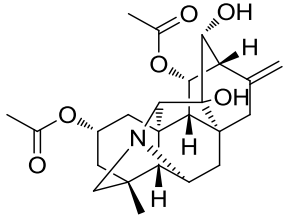
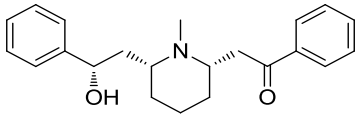
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 16 |  Paroxetine | 61869-08-7 | Approved, investigational | CHO cells | Slowing the deactivation time course, resulting in a tail crossover phenomenon when the tail currents, recorded in the presence and absence of paroxetine, were superimposed. | [43] |
| 17 |  Fluoxetine | 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 |  Sertraline | 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 $IC_{50}$ value of 50.2 μM. | [46] |
| 20 |  Hydrocortisone | 50-23-7 | Approved, vet approved | *Xenopus oocytes* | Suppressing the amplitude of Kv1.5 channel current with $IC_{50}$ value of 33.4 μM. | [46] |

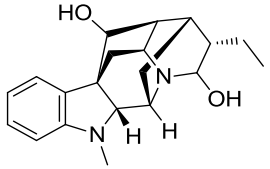
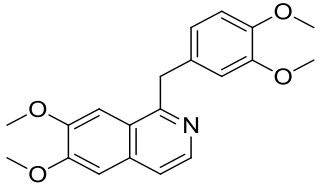
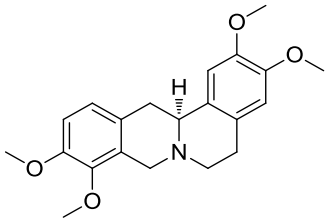
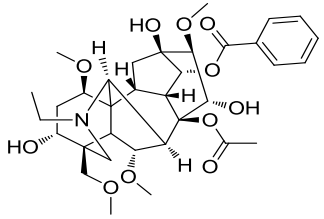
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 21 |  Spironolactone | 52-01-7 | Approved | Male Wistar rats | Shorting the $APD_{90}$ and increasing the expression of Kv1.5. | [47] |
| 22 |  Celecoxib | 169590-42-5 | Approved, investigational | Ltk- cells | Blocking *h*Kv1.5 channels with an $IC_{50}$ of 26.2 μM for the peak current and 5.5 μM for the current at the end of a 250 ms pulse to +60 mV. | [48] |
| 23 |  Bupivacaine | 38396-39-3 | Approved, investigational | Ltk- cells | Blocking the open of *h*Kv1.5 channels stereoselectively, the results showed the $K_d$value for *R*(+)-enantiomer (4.1 μM) 6-fold more potent than the *S*(-)-enantiomer (27.3 μM). | [49, 50] |
| 24 |  Propofol | 2078-54-8 | Approved, investigational, vet approved | CHO cells | Inducing a time-dependent decline of the *h*Kv1.5 current ($IC_{50}$: 62.9 μM) during depolarizing steps and slowed the time course of tail current decay upon repolarization. | [4] |
| 25 |  Midazolam | 59467-70-8 | Approved | HEK cells | Inhibited Kv1.5 current ($IC_{50}$: 17 μM) without influence on the half-maximal activation voltage of Kv1.5 channels. | [51] |

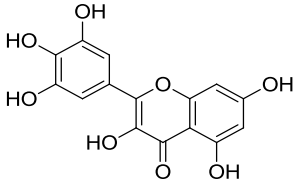
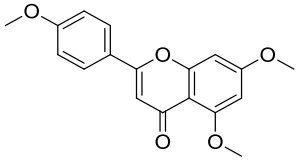
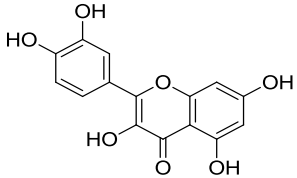
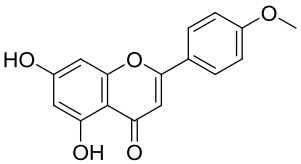
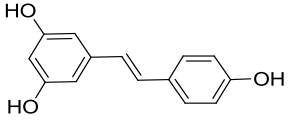
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 26 |  Tolbutamide | 64-77-7 | Approved, Investigational | insulin-secreting INS-1 cells | Activating Kv1.5 channel and the activation of secretion can be counteracted by an excessive stimulation of Kv channels in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

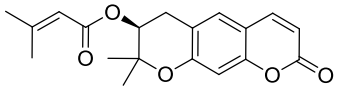
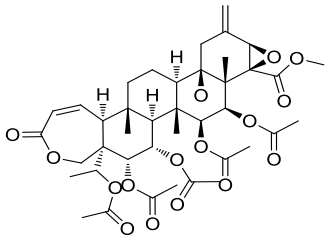
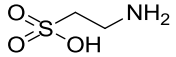
| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 31 |  BMS-394136 | 343246-73-1 | Phase 1 discontinued | Mouse fibroblast L929 cells | Showing excellent activity in blocking Kv1.5 ($IC_{50}$: 0.05 μM) and very good selectivity over *h*ERG, sodium and L-type calcium ion channels. | [57] |
| 32 |  BMS-919373 | 1272353-82-8 | Phase 1 Discontinued | Mammalian L-929 cells | Blocking *h*Kv1.5 current with $IC_{50}$ value of 0.05 μM with an acceptable *in vitro* selectivity and liability profile and a good pharmacokinetic profile across species. | [58] |
| 33 |  MK-0448 | 875562-81-5 | Phase 1 discontinued | 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 discontinued | CHO cells | Prolongating action potential duration (APD) and suppressed APs at high stimulation rates in sinus rhythm (SR), paroxysmal AF (*p*AF) tissue. | [60] |
| 35 |  LY294002 | 154447-36-6 | Experimental | CHO cells | Acting directly on *h*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 |  SSR149744C | 752253-75-1 | - | CHO cells | Inhibiting several potassium currents including $I_{Kr}$, $I_{Ks}$, $I_{K(ACh)}$ and $I_{Kv1.5}$ at the doses of 0.01-30 μM. | [61] |
| 37 |  CD-160130 | 1034194-07-4 | - | HEK cells | Inhibiting *h*Kv1.5 current slightly when specially blocked the Kv11.1 channel. | [62] |
| | ***Natural products*** | | **Type** | | | |
| 38 |  Debromoaplysiatoxin A | 2334247-91-3 | Terpenoid | CHO cells | Blocking Kv1.5 with an $IC_{50}$ value of 6.94 μM. | [63] |
| 39 |  Debromoaplysiatoxin B | 2334247-94-6 | Terpenoid | CHO cells | Blocking Kv1.5 with an $IC_{50}$ value of 0.30 μM. | [63] |

| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 40 |  Resiniferatoxin | 57444-62-9 | Terpenoid | C6 glioma cells | Inhibiting the *h*Kv1.5 current in time and dose-dependent manners | [64] |
| 41 |  Torilin | 13018-10-5 | Terpenoid | Ltk- cells | Inhibiting the *h*Kv1.5 current in time and voltage-dependent manners, with an $IC_{50}$ value of 2.51 μM 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 |  Guanfu base A | 1394-48-5 | Alkaloid | guinea pigs | Blocking *I*-Kv1.5 slight with the ratio of 20.6% at the dosage of 200 μM. | [66] |
| 43 |  Lobeline | 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 $IC_{50}$ value of 15.1 μM. | [67] |

| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 44 |  Ajmaline | 4360-12-7 | Alkaloid | *Xenopus oocytes* | Inhibiting Kv1.5 with an $IC_{50}$ of 1.70 μM in *Xenopus expression* system, resulting in a mild leftward shift of Kv1.5 activation curve. | [68] |
| 45 |  Papaverine | 58-74-2 | Alkaloid | Ltk- cells | Blocking *h*Kv1.5 channels and native *h*Kv1.5 channels in a concentration-, voltage-, state-, and time-dependent manner. | [69] |
| 46 |  Tetrahydropalmatine | 2934-97-6 | Alkaloid | HEK cells | Blocking Kv1.5 currents dose-dependently with an $IC_{50}$ value of 53.2 μM, inhibited the delayed rectifier effect of Kv1.5 resulting in a potential left shift of the inactivation curve. | [70] |
| 47 |  Aconitine | 302-27-2 | Alkaloid | *Xenopus laevis oocytes* | Producing a voltage-, time-, and frequency-dependent inhibition of Kv1.5 ($IC_{50}$: 0.796 μM). | [71] |

| No. | Name | CAS | Status | Model | Mechanism | Ref. |
|---|---|---|---|---|---|---|
| 48 |  Myricetin | 529-44-2 | Flavonoid | HEK cells | Inhibiting $I_{kur}$ and the expression of *h*Kv1.5 in a dose-, time- and frequency-dependent manner. | [72] |
| 49 |  Trimethylapigenin | 5631-70-9 | Flavonoid | HEK cells | Suppressing *h*Kv1.5 current in HEK 293 cell line ($IC_{50}$: 6.4 μM)and the ultra-rapid delayed rectify $K^+$ current$I_{Kur}$ in human atrial myocytes ($IC_{50}$: 8.0 μM) by binding to the open channels and showed a use- and frequency-dependent manner. | [73] |
| 50 |  Quercetin | 117-39-5 | Flavonoid | *Xenopus laevis*oocytes | Activating *h*Kv1.5 channels ($EC_{50}$: 37.8 μM) by interacting with key residue Ile 502 in S6 region. | [74] |
| 51 |  Acacetin | 480-44-4 | Flavonoid | HEK cells | Blocking open *h*Kv1.5 channels by binding to their S6 domain influenced by the interaction of V505A, I508A, and V512A. | [75] |
| 52 |  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 $IC_{50}$ value of 2.7 μM 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 | Polypeptide | T cell | Inhibiting *h*Kv1.5 current in a dose dependent manner. | [64] |
| 55 |  Correolide | 190017-00-6 | Nor-triterpenoid | CHO cells | Inhibiting Kv1.5 with an $IC_{50}$ of 1.77 μM and influenced by the mutations T480A, V505A, I508A, as well as V516A. | [78] |
| 56 |  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.

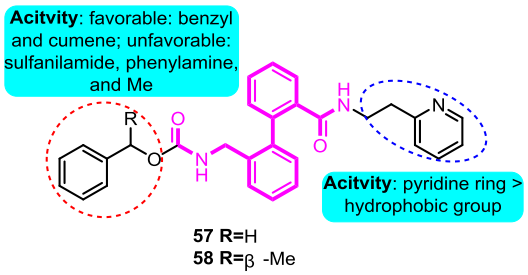



**Figure 3.**SAR of biphenyl derivatives.

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

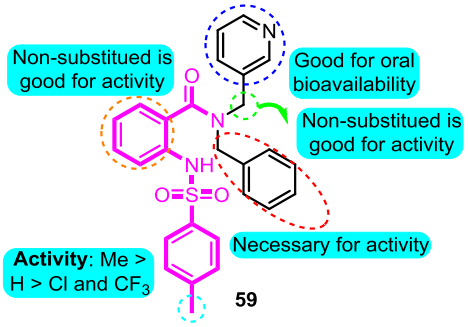



**Figure 4.**SAR of anthranilic amides.

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 ($IC_{50}$: 0.7 μM) with good oral bioavailability, however, no significant effect on the $I_{Kr}$ current of **59**was detected (**Figure4**).

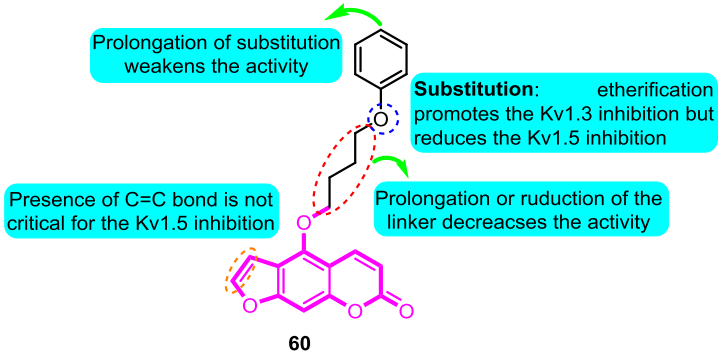



**Figure 5.**SAR of phenoxyalkoxypsoralen analogues.

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

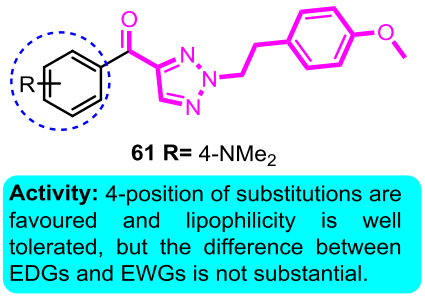
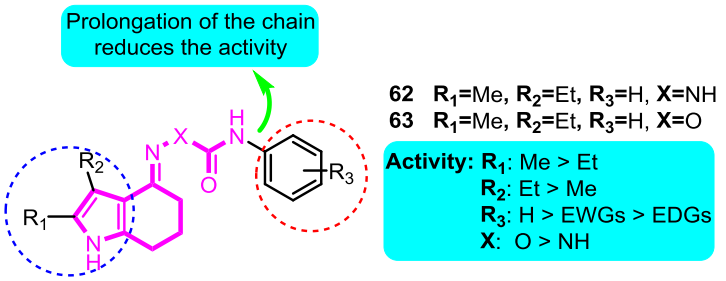



**Figure 6.**SAR of (2-phenethyl-2H-1,2,3-triazol-4-yl)(phenyl) methanones.

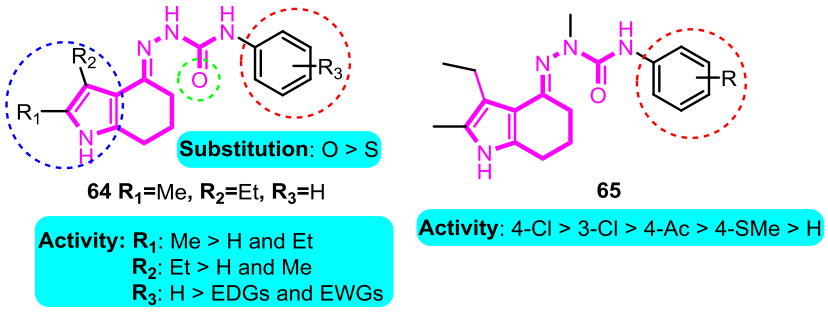
In 2006, Blass et al. [83] synthesized a cluster of (2-phenethyl-2H-1,2,3-triazol-4-yl) (phenyl) methanones and examined for utility as Kv1.5 channel blockers for the treatment of atrial fibrillation. The results showed that O substitution in the 4-position of the acetophenone-derived portion of the

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




43
44 **Figure 7.**SAR of tetrahydroindolone-derived carbamates.

45 Fluxe and co-workers [84] synthesized multiple tetrahydroindolone-derived
46 carbamates as the potent Kv1.5 blockers. The most promising analogues **62** and
47 **63**exhibited strongest Kv1.5 inhibitory effect with $IC_{50}$ values of 67 and 21 nM,
48 respectively. They were also very selective over *h*ERG (>450 fold) and L-type
49 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 ($IC_{50}$: 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**).

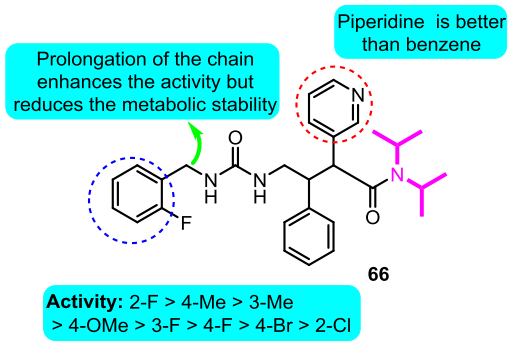



**Figure 9.**SAR of diisopropyl amide derivaitives.

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 ($IC_{50}$: 150 nM) (**Figure 9**).

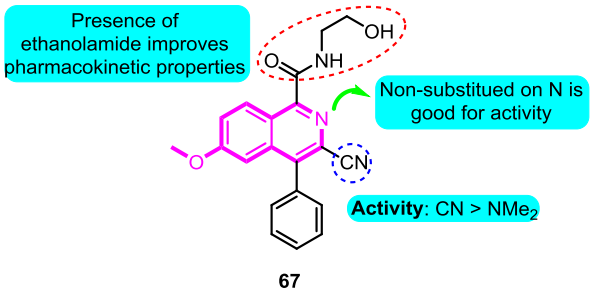



**Figure 10.**SAR of isoquinoline-3-nitriles.

Trotter and co-workers [87] design and synthesized a group of isoquinoline-3-nitriles as orally Kv1.5 antagonists for the treatment of AF. The ethanolamide derivative**67**exhibited improved potency (Kv1.5 HT-Clamp $IC_{50}$: 60 nM), excellent selectivity versus *h*ERG, and good pharmacokinetic properties. Rat EP experiments confirmed that the compound potently increased ARP without significant effects on AVRP (**Figure 10**).

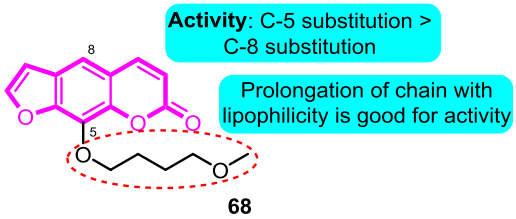



**Figure 11.**SAR of psoralen derivatives.

In 2007, Eun et al. [88] synthesized multiple psoralen derivatives as *h*Kvl.5 channel blocker. Among them, compound**68** was the most potent in blocking *h*Kv1.5 ($IC_{50}$: 27.4 nM), much stronger than the lead compound psoralen. Compound **68**accelerated the inactivation kinetics of the *h*Kvl.5 channel, slowed the deactivation kinetics of *h*Kv1.5 current resulting in a tail crossover phenomenon. Compound **68**inhibited *h*Kvl.5 current in a use-dependent manner (**Figure 11**).

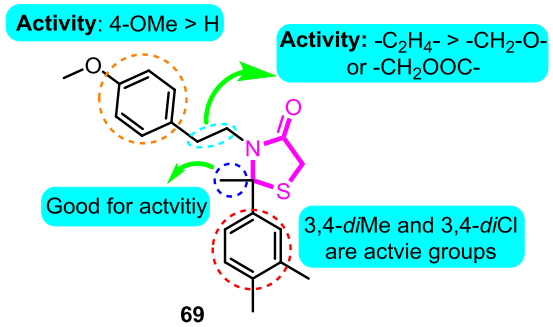



**Figure 12.**SAR of thiazolidine derivatives.

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 $IC_{50}$ value of 69 nM(**Figure 12**).

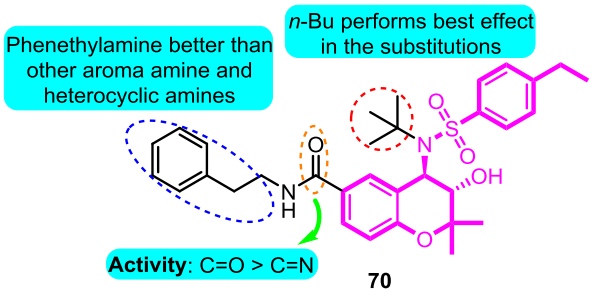



**Figure 13.**SAR of benzopyran sulfonamides.

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 ($IC_{50}$: 57 nM), and the moderate inhibition (35%) of *h*ERG at the concentration of 10 μM (**Figure 13**).

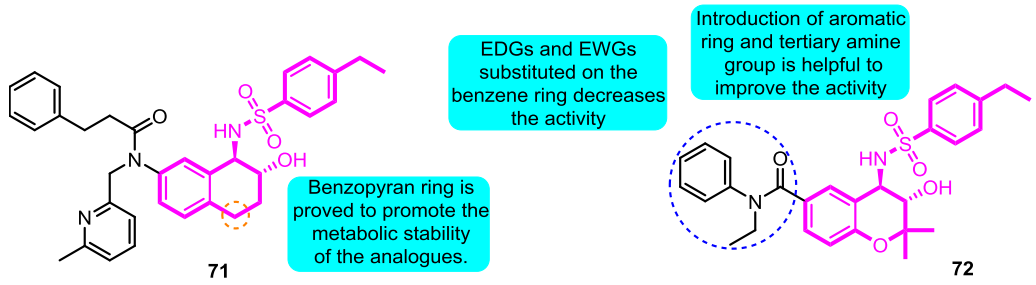



**Figure 14.**SAR of thiazolidine derivatives.

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 $IC_{50}$ values for 46 and 378 nM in the inhibition of current in L-929 cells model, respectively. Additionally, at the concentration of 1 μM, compound **72**displayed the most significant inhibitory effect in current in L-929 cells with the inhibitory ratio for 89% (**Figure 14**).

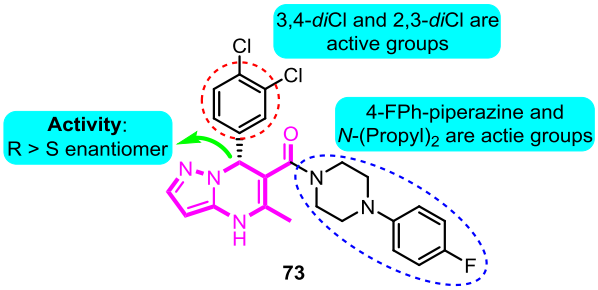



**Figure 15.**SAR of dihydropyrazolopyrimidine derivatives.

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

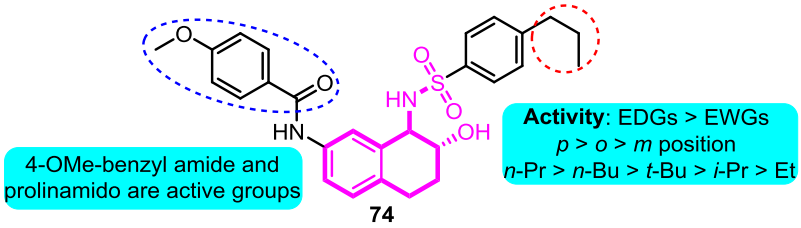
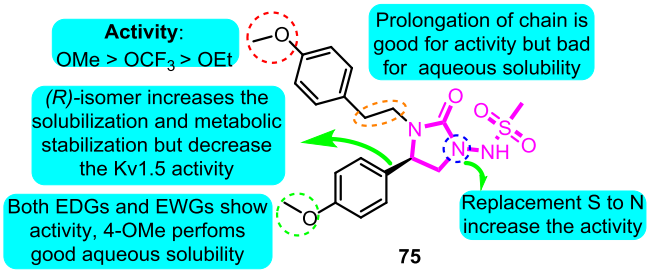



**Figure 16.**SAR of aryl sulfonamido tetralin derivatives.

In 2008, Gross and co-workers [92] synthesized aryl sulfonamido tetralin as Kv1.5 inhibitor according to the basis of previous work. Among the productions,

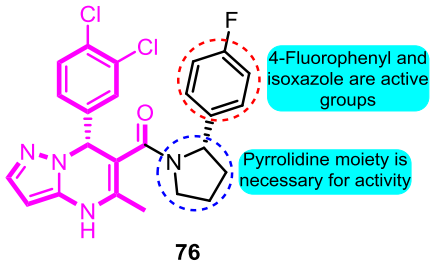
112 compound **74**exhibited remarkable Kv1.5 inhibition with $IC_{50}$ value for 90 nM, in
113 addition, moderate hERG inhibition was detected at the dose of 10 μM (39%),
114 indicating the potential of further development of clinical candidates (**Figure 16**).




115

116 **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 $IC_{50}$ values for compound **75** in Kv1.5, *h*ERG, 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**).




125

126 **Figure 18.** SAR of pyrazolodihydropyrimidines.

127 In 2010, Lloyd and co-workers [58] developed a series of
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 ($IC_{50}$: 50 nM) and very good selectivity over
131 *h*ERG, sodium and L-type calcium ion channels with good pharmacokinetic
132 parameters (**Figure 18**).

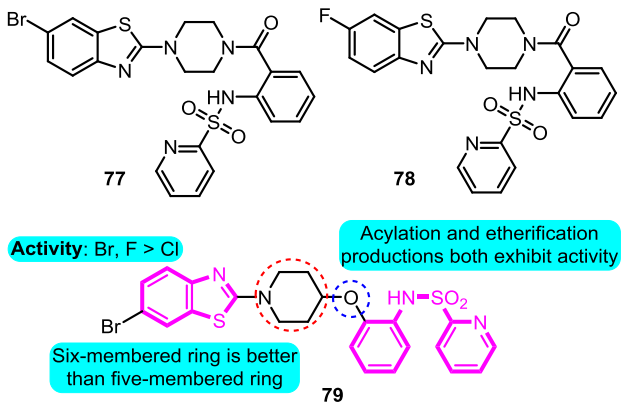



**Figure 19.** SAR of heteroarylsulfonamides.

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**).

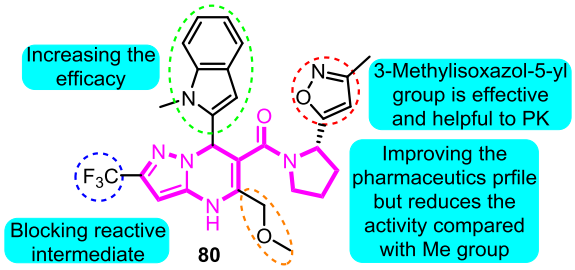



**Figure 20.** SAR of dihydropyrazolo[1,5-a]pyrimidine derivatives.

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 $IC_{50}$ for 0.15 μM and *h*ERG for $IC_{50}$> 10 μM. Furthermore, favorable pharmacokinetic properties in rats and dogsof 8**0**were 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**).

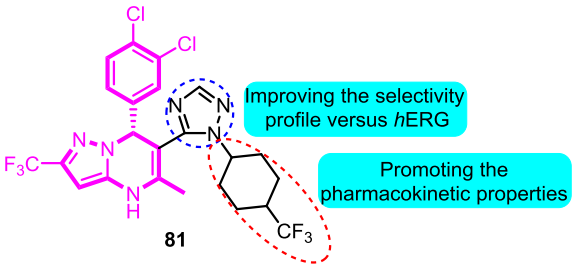


**Figure 21.** SAR of trifluoromethylcyclohexyl triazole analogues.

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 ($IC_{50}$: 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**).

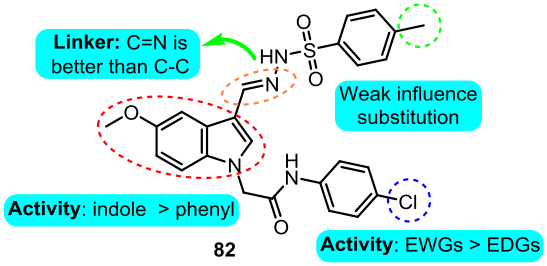



**Figure 22.** SAR of indole derivatives.

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 $IC_{50}$ values of 52.6, 0.51 and 418.35 μM, respectively, which displayed remarkable selectivity and ameliorating effects on AERP and VERP (**Figure 22**).

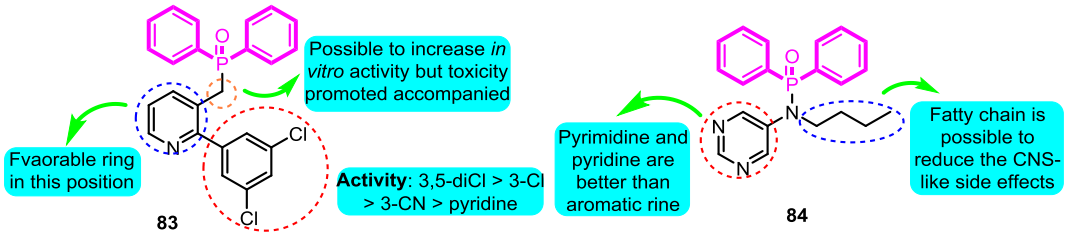
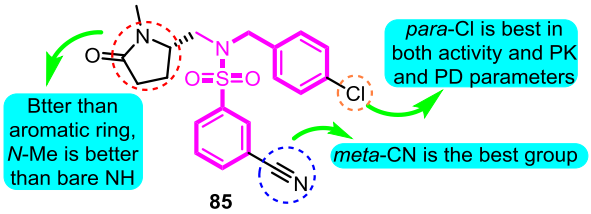



**Figure 23.** SAR of diphenylphosphinic amides and diphenylphosphine oxides.

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 $IC_{50}$ of 0.08 μM 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,

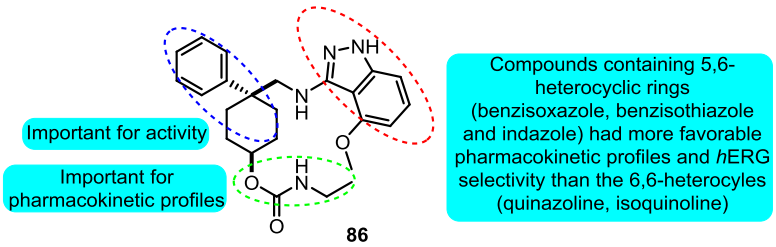
169 conversely, the derivative **84** was regarded as the hopeful compound for further
170 development with Kv1.5 $IC_{50}$, IKs, $C_{eu20}$, $QT_{max}$ change values for 1 μM, >33%, 0.6
171 μM, <10%, respectively.




172

173 **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 $IC_{50}$ value of 0.21 μM, andcaused a
177 marked increase in the atrium ERP with a $C_{eu20}$ of 0.35 μM, which was at the same
178 order of magnitude as the $IC_{50}$ value from the human cellular assay. The human
179 *h*ERG channel was blocked by compound **85** with an $IC_{50}$ value of 30 μM,
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**).




185

186 **Figure 25.** SAR of phenethylaminoheterocycles.

187 Johnson et al. [100] synthesized phenethylaminoheterocycles and assayed for
188 inhibition of the Kv1.5 potassium ion channel as a potential approach to the
189 treatment of atrial fibrillation. Combination of the indazole with a
190 cyclohexane-based template gave the most promising derivative **86**(Kv1.5 $IC_{50}$: 138
191 nM) which demonstrated significant prolongation of AERP in the rabbit

pharmacodynamic model(**Figure 25**).

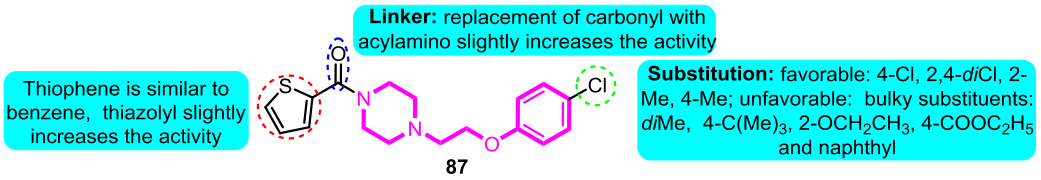



**Figure 26.** SAR of 1-aryloxyethyl piperazine derivatives.

Guo and colleagues [101] prepared a series of 1-aryloxyethyl piperazine derivatives as Kv1.5 potassium channel inhibitors. The most potent compound **87**exerted significant activity on *h*Kv1.5 ($IC_{50}$: 0.72 μM), balanced Log D and permeability. In addition, comparable *in vivo* potency with sotalol and dronedarone and remarkable safety in rats of compound **87**was detected as well (**Figure 26**).

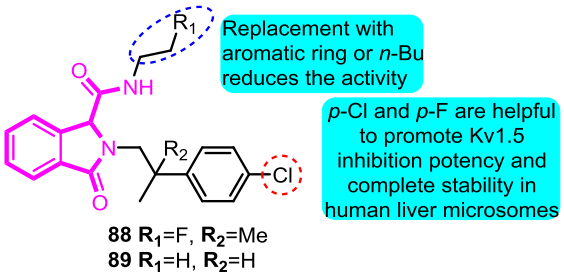



**Figure 27.** SAR of isoindolinones.

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 $IC_{50}$ values of 0.4 and 0.7 μM on Kv1.5, respectively. The above mentioned two compounds were found to have desirable *in vivo* PK properties in mouse model (**Figure 27**).

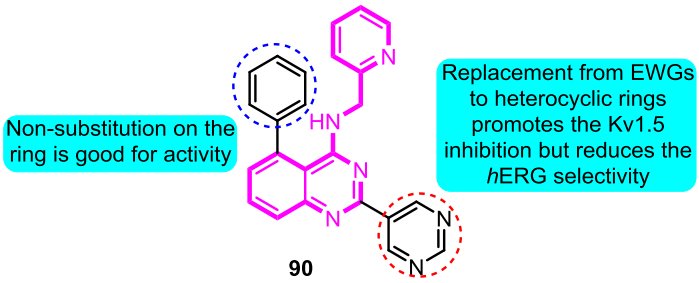



**Figure 28.** SAR of phenylquinazoline derivatives.

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 $IC_{50}$: 90 nM, *h*ERG inhibition: 43% at 10 μM) 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**).

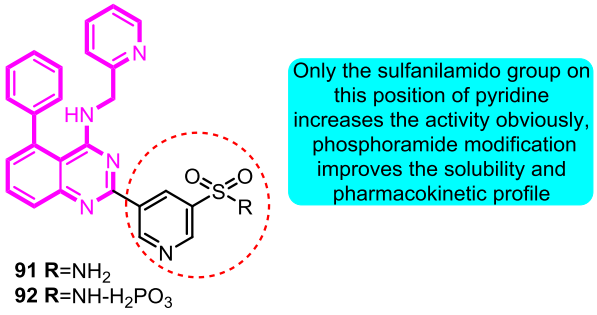



**Figure 29.** SAR of phenylquinazoline sulfonamide derivatives.

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] pyridine-3-sulfonamide (**92**) was identified as the lead compound in this series with good selectivity over *h*ERG (Kv1.5 $IC_{50}$: 50 nM, *h*ERG $IC_{50}$: 1.9 μM). Compound **91**exhibited robust effects in rabbit and canine pharmacodynamic models and an acceptable cross-species pharmacokinetic profile which was then advanced as a clinical candidate. Further optimization of **91**to mitigate pH-dependent absorption resulted in identification of the corresponding phosphoramide prodrug (**92**) with an improved solubility and pharmacokinetic profile(**Figure 29**).

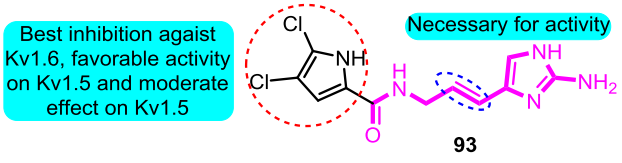



**Figure 30.** SAR of oroidin derivatives.

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 $IC_{50}$ values between 1.4 and 6.1 mM against Kv1.3, Kv1.4, Kv1.5 and Kv1.6 channels (Kv1.5 $IC_{50}$: 6.1 μM) (**Figure 30**).

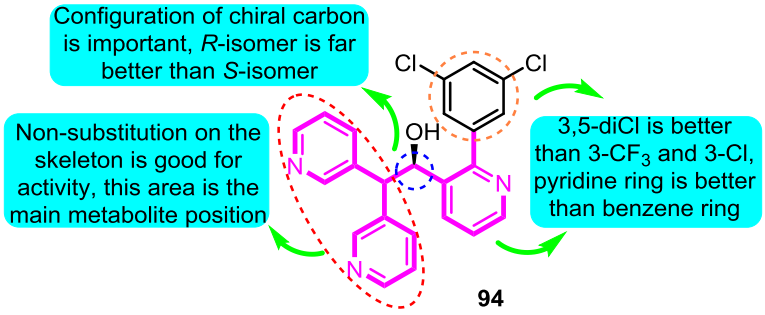



**Figure 31.** SAR of oroidin MK-1832.

Wolkenberg et al. [105] told the story of the development of prospective candidate MK-1832 (**94**)(**Figure 31**). Based on the structure of MK-0448, a cluster of derivatives were synthesized and tested the Kv1.5 inhibitory effect and *in vivo* and *in vitro* toxicity. MK-1832 (**94**) was considered to be best derivative with pharmacological parameters including Kv1.5, $I_{kur}$, $I_{kr}$(*h*ERG) $IC_{50}$ values for 29, 11, 128000 nM, resepectively, and pharmacokinetic parameters including dog in vivo atrial refractory period $EC_{10}$ for 14 nM and threshold change in ventricular refractory period > 25 μM.

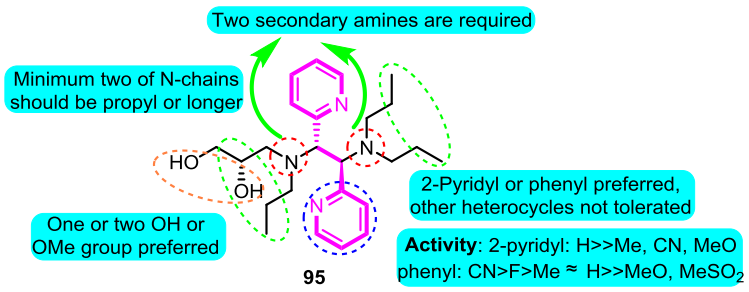
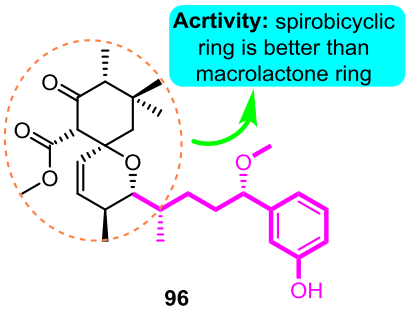



**Figure 32.** SAR of 1,2-bis(aryl)ethane-1,2-diamines.

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

252 in human atrial myocytes ($IC_{50}$: 1.7 μM, $I_{Kur}$ $IC_{50}$: 60 nM) and based on the PD data,
253 the estimated dose to man was 700 mg/day (**Figure 32**).




96

254
255 **Figure 33.** SAR of aplysiatoxin derivatives.

256 Recently, natural products with novel structural motif as Kv1.5 inhibitor also
257 gain progress in this field. In the sequence of the isolation of
258 compounddebromoaplysiatoxin A (**38**) and debromoaplysiatoxin 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 ($IC_{50}$: 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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## Conflict of interest

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

## Abbreviations

AF: atrial fibrillation;

BLAST: Basic Local Alignment Search Tool;

298 $C_{eu20}$: 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 $IC_{50}$: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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