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Review

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

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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 α -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.

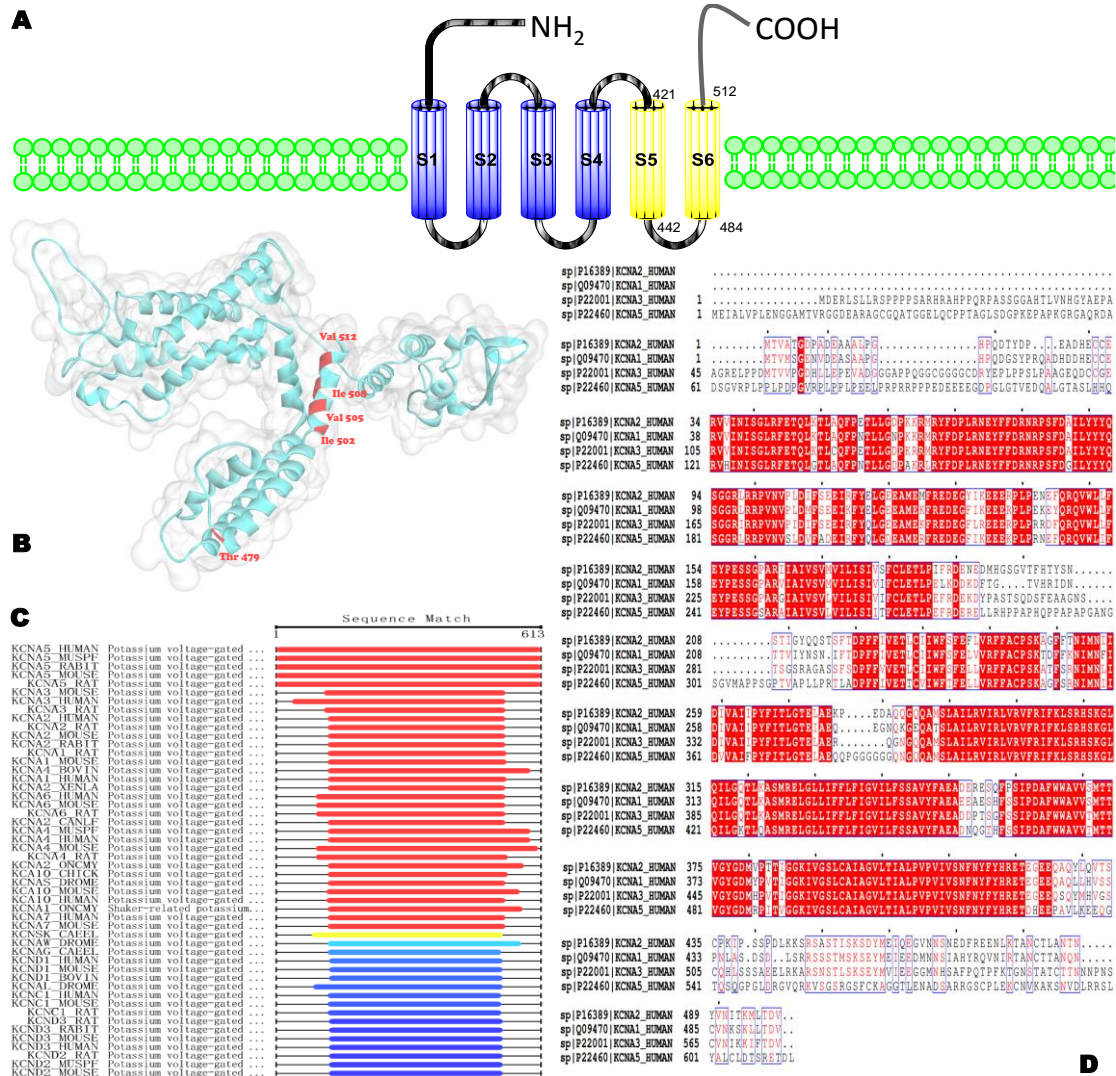


Figure 1. (A) Schematic representation of *hKv1.5* α -subunit with the sequence of S6 region listed; (B) Homologous model of Kv1.5 (Q61672) with the range of 67.2% for sequence of Kv1.5 getting from the SWISS-MODEL database, some of the residues are slightly different with the contents from published 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 play 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 piperidine (lobeline, CD-160130, bupivacaine, paroxetine and donepezil) is important because these moieties usually influence the acidification 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].

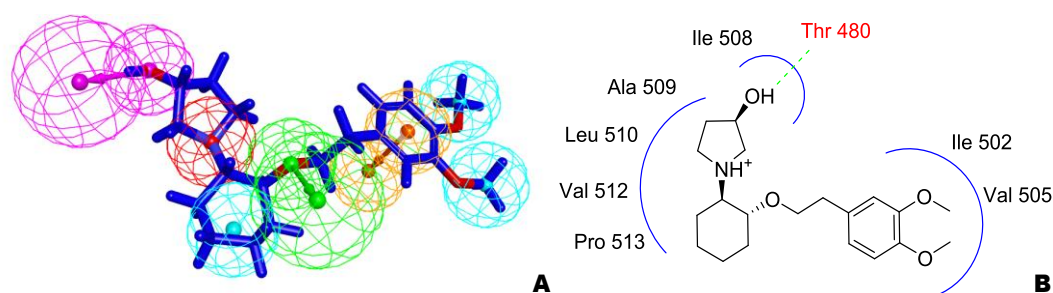


Figure 2.(A) Pharmacophore model of vernakalant (cyan ball: hydrophobic center; yellow ball: aromatic center; green ball: hydrogen bond receptor; pink ball: hydrogen bond donor; red ball: ionizable positive center); (B) potential binding domain of vernakalant in Kv1.5 (H-bond is expressed as green dashed).

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, the selectivity 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 by Kv11.1 [22], which are the important targets influencing prolong QT syndrome and torsade de pointes attributed to the gain-of-function mutations being 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⁺ channel for Kv1.5, some of which also block Kv1.3 channels: e.g. 4-aminopyridine (**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 enhance the 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.

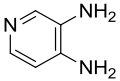
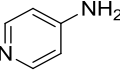
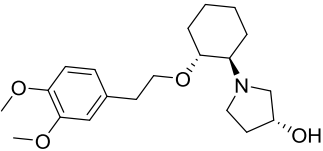
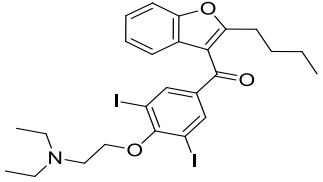
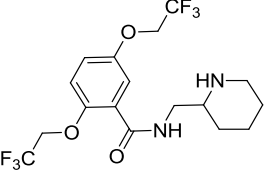
A variety of natural products have been proved to modulate Kv1.5, the exploration of novel skeleton could be helpful to the current dilemma. Among the isolated compounds, terpenoids (38-41), alkaloids (42-47) and flavonoids (48-50) are the main types. Terpenoids are widely reported to inhibit potassium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

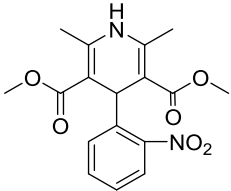
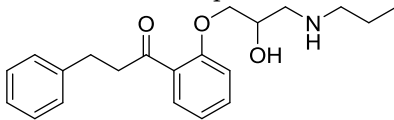
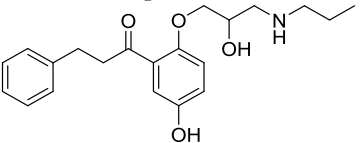
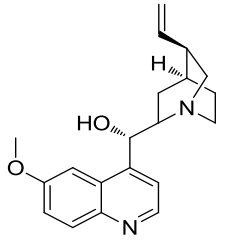
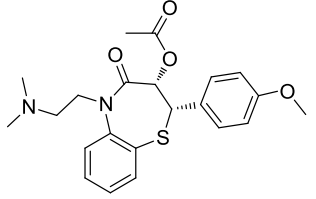
Synthetic Kv1.5 inhibitors and SAR investigations

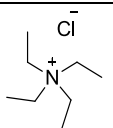
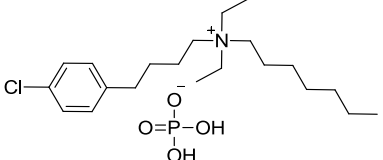
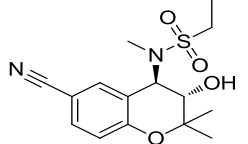
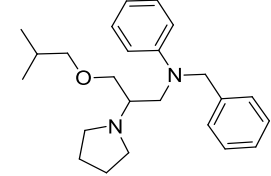
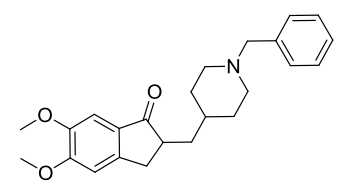
In this part, we collated the information about chemical synthesis, pharmacological properties and SAR investigations in the published literatures ranging from 2003 to 2019 and summarized them with a timeline clue. The previous work was briefly introduced in the description about the potential synthetic 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)

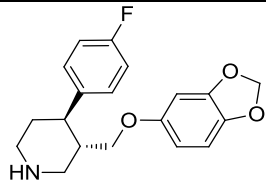
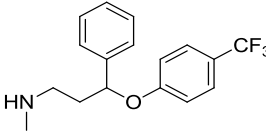
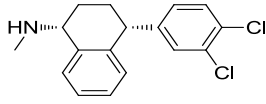
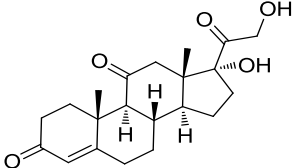
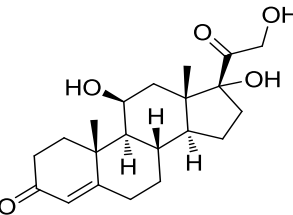
and phenylquinazoline(90-92).

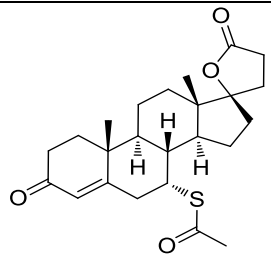
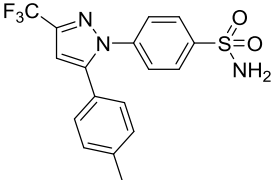
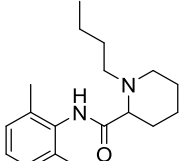
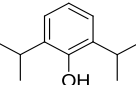
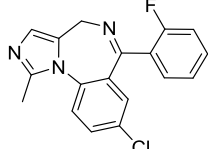
Table 1. Active KV 1.5 modulators.

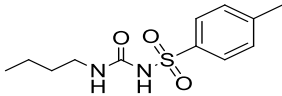
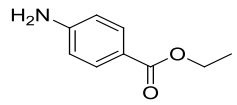
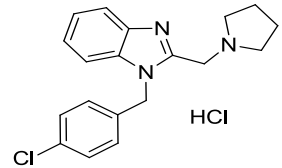
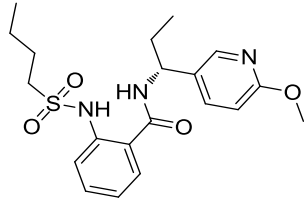
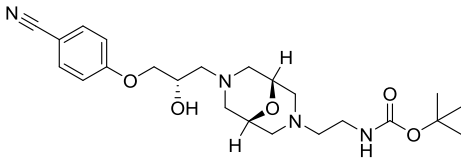
No	Name	CAS	Status	Model	Mechanism	Ref.
<i>Clinical cardiovascular drugs</i>						
1	 3,4-Diaminopyridine	54-96-6	Approved	Smooth muscle cells	Blocking <i>hKv1.5</i> current with a threshold for activation near -45 mV.	[30]
2	 4-Aminopyridine	504-24-5	Approved	HEK cells	Inhibiting <i>hKv1.5</i> current 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	<i>Xenopus laevis</i> oocytes	Producing open-channel block of Kv1.5 with sensitivity by interacting with key residues including Asp 469, Val 481 and Ile 502 in the S6 region of Kv1.5.	[34]

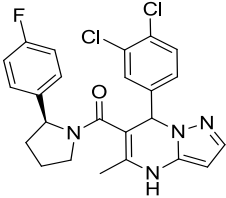
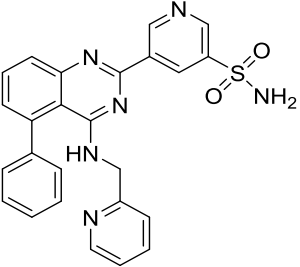
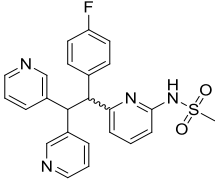
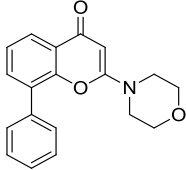
No	Name	CAS	Status	Model	Mechanism	Ref.
6	 Nifedipine	21829-25-4	Approved	HEK cells	Blocking <i>hKv1.5</i> channels with K_{aof} of 6.3 μ M, affected by mutations like Arg 487 similar to those known to affect outer pore C-type inactivation.	[35]
7	 Propafenone	54063-53-5	Approved	Ltk ⁻ cells	Inhibiting <i>hKv1.5</i> current with K_a value of 9.2 μ M, showing time-dependent and dose-dependent manners simultaneously.	[36]
8	 5-Hydroxy-propafenone	86384-10-3	-	Ltk ⁻ cells	Inhibiting <i>hKv1.5</i> current with K_a value of 4.4 μ M, 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 μ M) with an equivalent electrical distance in the steady state.	[37]
10	 Diltiazem	42399-41-7	Approved, investigational	CHO cells	Blocking <i>hKv1.5</i> channels, in a frequency-dependent manner exhibiting a biphasic dose-response curve (IC_{50} : 4.8 nM and 42.3 μ M) by binding to the open and the inactivated state of the channels.	[38]

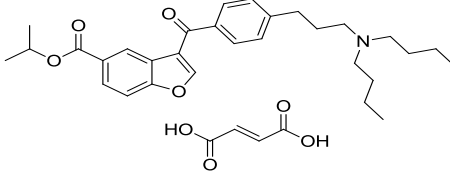
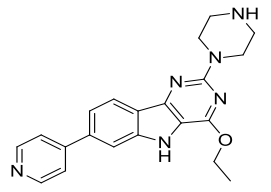
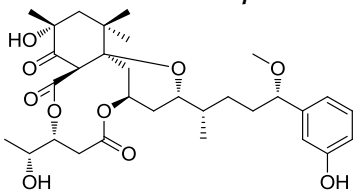
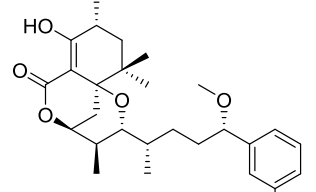
No	Name	CAS	Status	Model	Mechanism	Ref.
11	 Tetraethylammonium	66-40-0	Experimental, investigational	BT-474 breast cancer cell	Blocking <i>hKv1.5</i> channels in a delayed rectifier manner	[39]
12	 Clofilium	68379-03-3	-	CHO cells	Inhibiting <i>hKv1.5</i> current with concentration-dependent acceleration of the apparent channel inactivation in both outside-out and inside-out patches.	[40]
13	 Chromanol 293B	163163-23-3	-	CHO cells	Blocking <i>hKv1.5</i> 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 <i>hKv1.5</i> channel current with the IC_{50} value of 6.6 μ M.	[42]
<i>Other clinical drugs</i>						
15	 Donepezil	120014-06-4	Approved	HEK cells	Resulting in a rapid and reversible block of <i>Kv1.5</i> currents (IC_{50} : 72.5 μ M) with a significant delay in the duration of activation and deactivation, and the outer mouth region was proved to be the target site.	[15]

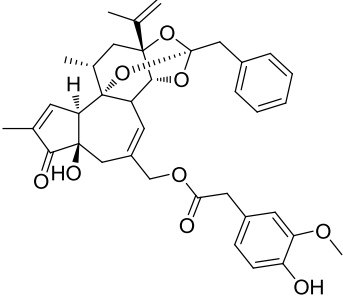
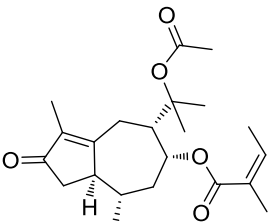
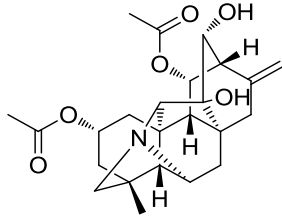
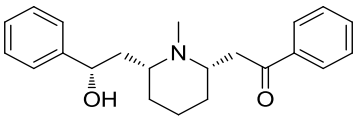
No	Name	CAS	Status	Model	Mechanism	Ref.
16	 Paroxetine	61869-08-7	Approved, investigational	CHO cells	Slowing the deactivation time course, resulting in a tail crossover phenomenon when the tail currents, recorded in the presence and absence of paroxetine, were superimposed.	[43]
17	 Fluoxetine	54910-89-3	Approved, vet approved	Human PSMCs	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	<i>Xenopus oocytes</i>	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	<i>Xenopus oocytes</i>	Suppressing the amplitude of Kv1.5 channel current with IC ₅₀ value of 33.4 μM.	[46]

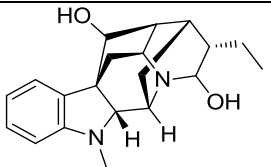
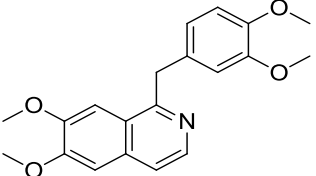
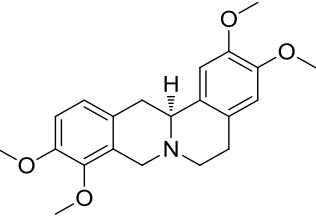
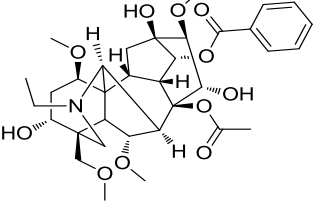
No	Name	CAS	Status	Model	Mechanism	Ref.
21	 Spironolactone	52-01-7	Approved	Male Wistar rats	Shorting the APD ₉₀ and increasing the expression of Kv1.5.	[47]
22	 Celecoxib	169590-42-5	Approved, investigational	Ltk ⁻ cells	Blocking <i>h</i> Kv1.5 channels with an IC ₅₀ of 26.2 μM for the peak current 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 <i>h</i> Kv1.5 channels stereoselectively, the results showed the K _a value for <i>R</i> (+)-enantiomer (4.1 μM) 6-fold more potent than the <i>S</i> (-)-enantiomer (27.3 μM).	[49, 50]
24	 Propofol	2078-54-8	Approved, investigational, vet approved	CHO cells	Inducing a time-dependent decline of the <i>h</i> 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]

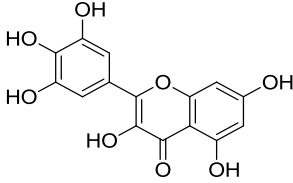
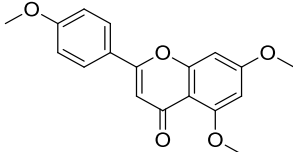
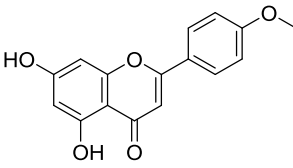
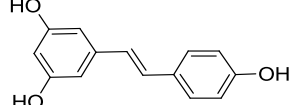
No	Name	CAS	Status	Model	Mechanism	Ref.
26	 Tolbutamide	64-77-7	Approved, Investigational	insulin-secreting INS-1 cells	Activating Kv1.5 channel and the activation of secretion can be counteracted by an excessive stimulation of Kv channels in INS-1 cells which shortened the Ca ²⁺ signal and confines insulin secretion.	[52]
27	 Benzocaine	94-09-7	Approved	Ltk ⁻ cells	Blocking <i>h</i> Kv1.5 channels in a voltage-dependent manner and modified the voltage-dependence of channel activation	[53]
<i>Drugs in development</i>						
28	 Clemizole hydrochloride	1163-36-6	Phase 2 Clinical	HEK cells	Decreasing <i>I</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 <i>h</i> 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 <i>h</i> Kv1.5 current with IC ₅₀ value of 27 μM with a slight decrease at higher frequency.	[56]

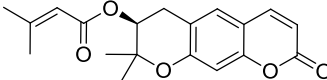
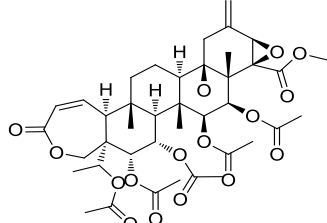
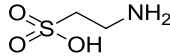
No	Name	CAS	Status	Model	Mechanism	Ref.
31	 BMS-394136	343246-73-1	Phase 1 discontinued	Mouse fibroblast L929 cells	Showing excellent activity in blocking Kv1.5 (IC ₅₀ : 0.05 μM) and very good selectivity over <i>h</i> ERG, sodium and L-type calcium ion channels.	[57]
32	 BMS-919373	1272353-82-8	Phase 1 Discontinued	Mammalian L-929 cells	Blocking <i>h</i> Kv1.5 current with IC ₅₀ 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 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 (<i>p</i> AF) tissue.	[60]
35	 LY294002	154447-36-6	Experimental	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	 <p>SSR149744C</p>	752253-75-1	-	CHO cells	Inhibiting several potassium currents including I_{K_T} , I_{K_S} , $I_{K(ACh)}$ and $I_{Kv1.5}$ at the doses of 0.01-30 μ M.	[61]
37	 <p>CD-160130</p>	1034194-07-4	-	HEK cells	Inhibiting $hKv1.5$ current slightly when specially blocked the $Kv11.1$ channel.	[62]
	<i>Natural products</i>		Type			
38	 <p>Debromoaplysiatoxin A</p>	2334247-91-3	Terpenoid	CHO cells	Blocking $Kv1.5$ with an IC_{50} value of 6.94 μ M.	[63]
39	 <p>Debromoaplysiatoxin B</p>	2334247-94-6	Terpenoid	CHO cells	Blocking $Kv1.5$ with an IC_{50} value of 0.30 μ M.	[63]

No	Name	CAS	Status	Model	Mechanism	Ref.
40	 Resiniferatoxin	57444-62-9	Terpenoid	C6 glioma cells	Inhibiting the <i>hKv1.5</i> current in time and dose-dependent manners	[64]
41	 Torilin	13018-10-5	Terpenoid	Ltk cells	Inhibiting the <i>hKv1.5</i> current in time and voltage-dependent manners, with an IC_{50} value of 2.51 μ M at +60 mV, accelerated the inactivation kinetics of the <i>hKv1.5</i> channel, and slowed the deactivation kinetics of the <i>hKv1.5</i> current, resulting in a tail crossover phenomenon.	[65]
42	 Guanfu base A	1394-48-5	Alkaloid	guinea pigs	Blocking <i>I-Kv1.5</i> slight with the ratio of 20.6% at the dosage of 200 μ M.	[66]
43	 Lobeline	90-69-7	Alkaloid	HEK cells	Accelerating the decay rate of <i>Kv1.5</i> inactivation, decreasing the current amplitude at the end of the pulse in a concentration-dependent manner with a IC_{50} value of 15.1 μ M.	[67]

No	Name	CAS	Status	Model	Mechanism	Ref.
44	 Ajmaline	4360-12-7	Alkaloid	<i>Xenopus oocytes</i>	Inhibiting Kv1.5 with an IC ₅₀ of 1.70 μM in <i>Xenopus expression</i> system, resulting in a mild leftward shift of Kv1.5 activation curve.	[68]
45	 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	 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	<i>Xenopus laevis oocytes</i>	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 $hKv1.5$ in a dose-, time- and frequency-dependent manner.	[72]
49	 Trimethylapigenin	5631-70-9	Flavonoid	HEK cells	Suppressing $hKv1.5$ current in HEK 293 cell line (IC_{50} : $6.4 \mu M$) and the ultra-rapid delayed rectify K^+ current I_{Kur} in human atrial myocytes (IC_{50} : $8.0 \mu M$) by binding to the open channels and showed a use- and frequency-dependent manner.	[73]
50	 Quercetin	117-39-5	Flavonoid	<i>Xenopus laevis</i> oocytes	Activating $hKv1.5$ channels (EC_{50} : $37.8 \mu M$) by interacting with key residue Ile 502 in S6 region.	[74]
51	 Acacetin	480-44-4	Flavonoid	HEK cells	Blocking open $hKv1.5$ channels by binding to their S6 domain influenced by the interaction of V505A, I508A, and V512A.	[75]
52	 Resveratrol	501-36-0	Phenol	Human PSMCs	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 <i>hKv1.5</i> 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 <i>hKv1.5</i> channel, resulting in a tail crossover phenomenon.	[77]
54	Kaliotoxin	145199-73-1	Polypeptide	T cell	Inhibiting <i>hKv1.5</i> current in a dose dependent manner.	[64]
55	 Correolide	190017-00-6	Nor-triterp enoid	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]

1 (86-88) have been reported to be effective in inhibiting Kv1.5, suggesting potential
 2 directions for the investigation about the Kv1.5 inhibitors in the future. It is
 3 noteworthy that researches from Bristol-Myers Squibb paid great efforts in this
 4 field with a lot of data about pharmacology and pharmacokinetics of active
 5 compounds in blocking Kv1.5, increasing the possibility that we human beings
 6 conquer the diseases targeting Kv1.5.

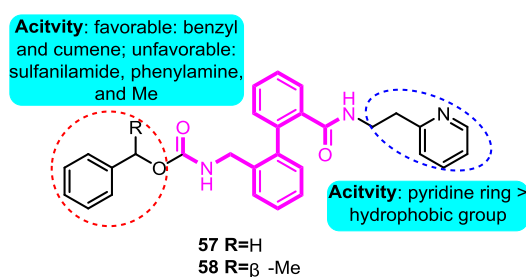


Figure 3.SAR of biphenyl derivatives.

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(IC₅₀: 0.7 μM) and 58(IC₅₀: 0.16
 12 μM)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).

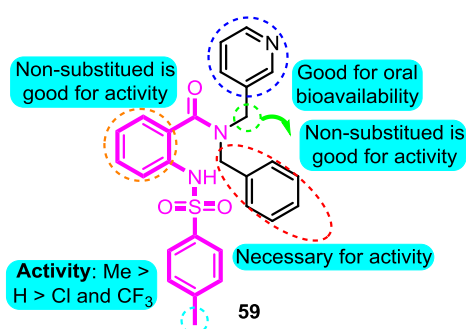
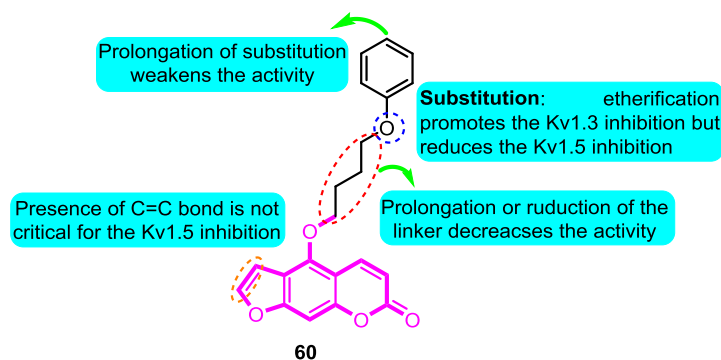


Figure 4.SAR of anthranilic amides.

17 In 2004, Peukert et al. [81] synthesized several anthranilic amides as novel
 18 blockers of the Kv1.5 channel. The most hopeful analogue 59 showed moderate
 19 Kv1.5 inhibition (IC₅₀: 0.7 μM) with good oral bioavailability, however, no
 20 significant effect on the I_{Kr} current of 59was detected (Figure4).



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Figure 5. SAR of phenoxyalkoxy psoralen analogues.

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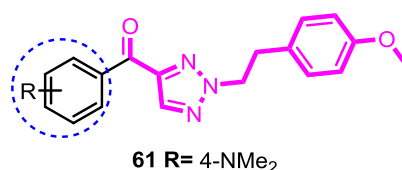
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Inspired from the precursor 5-methoxy psoralen isolated from *Rutagraveolens*, Schmitz and colleagues [82] prepared a series of phenoxyalkoxy psoralen analogues and evaluated their voltage-gated ion channel blocker potency. The most potent and “druglike” 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 EC₅₀ 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**).



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

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

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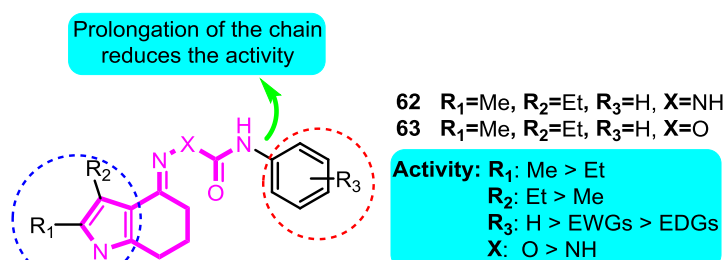
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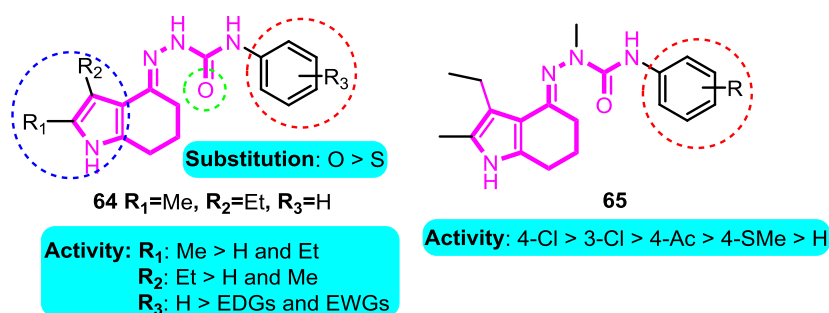
In 2006, Blass et al. [83] synthesized a cluster of (2-phenethyl-2H-1,2,3-triazol-4-yl) (phenyl) methanones and examined for utility as Kv1.5 channel blockers for the treatment of atrial fibrillation. The results showed that O substitution in the 4-position of the acetophenone-derived portion of the

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



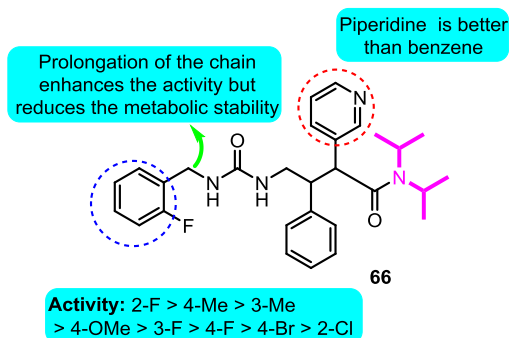
44 Figure 7. SAR of tetrahydroindolone-derived carbamates.

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) (Figure 7).



51 Figure 8. SAR of tetrahydroindolone-derived 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 μ M 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 (Figure 8).

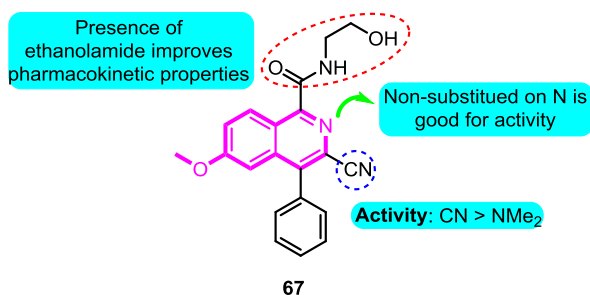


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Figure 9. SAR of diisopropyl amide derivatives.

60 Based on a diisopropyl amide scaffold, a series of potent Kv1.5 ion channel
 61 antagonists were synthesized by Nanda and colleagues [86]. The most active
 62 derivative **66**, which was a single active enantiomer of the diastereomerically pure
 63 racemic analog, exhibited significant atrial-selective effects in an *in vivo* model (IC₅₀:
 64 150 nM) (**Figure 9**).

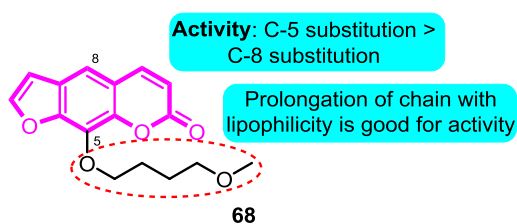


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Figure 10. SAR of isoquinoline-3-nitriles.

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

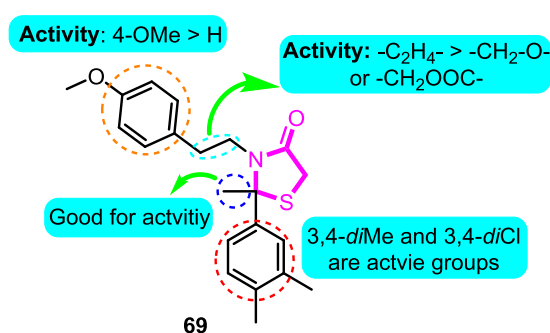


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Figure 11. SAR of psoralen derivatives.

75 In 2007, Eun et al. [88] synthesized multiple psoralen derivatives as *hKv1.5*
 76 channel blocker. Among them, compound **68** was the most potent in blocking
 77 *hKv1.5* (IC_{50} : 27.4 nM), much stronger than the lead compound psoralen.
 78 Compound **68** accelerated the inactivation kinetics of the *hKv1.5* channel, slowed
 79 the deactivation kinetics of *hKv1.5* current resulting in a tail crossover
 80 phenomenon. Compound **68** inhibited *hKv1.5* current in a use-dependent manner
 81 (**Figure 11**).

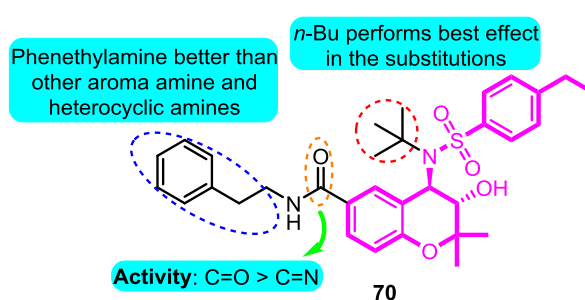


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Figure 12. SAR of thiazolidine derivatives.

84 Jackson and co-workers [89] prepared several classes of thiazolidine-based
 85 *Kv1.5* blockers. The most promising analogue **69** derived from
 86 3,4-dimethylacetophenone exhibited the strongest inhibitory effect with an IC_{50}
 87 value of 69 nM (**Figure 12**).

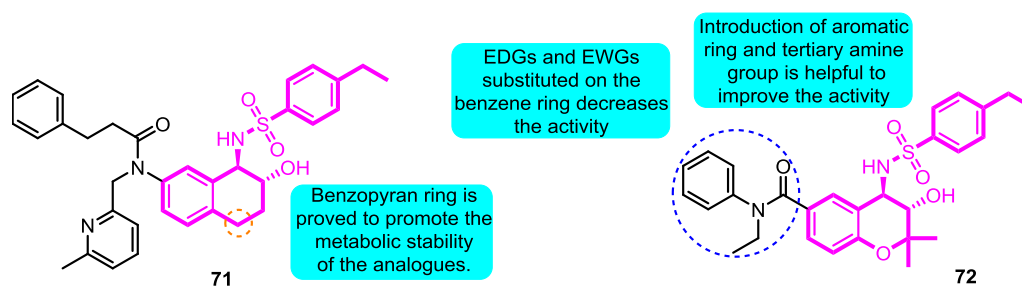


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Figure 13. SAR of benzopyran sulfonamides.

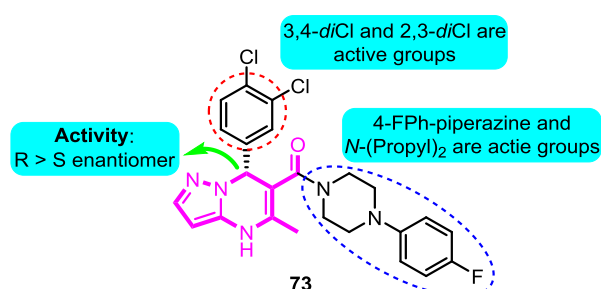
90 Lloyd et al. [90] synthesized a series of benzopyran sulfonamides and
 91 determined *Kv1.5* potassium channel blocking effects. Among the productions,
 92 derivative **70** exhibited the most significant activity (IC_{50} : 57 nM), and the moderate
 93 inhibition (35%) of *hERG* at the concentration of 10 μ M (**Figure 13**).



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Figure 14. SAR of thiazolidine derivatives.

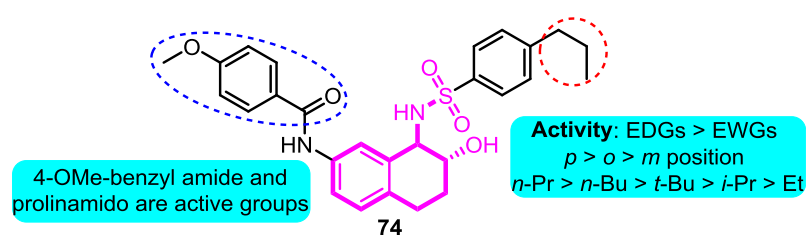
96 In 2008, the benzopyran sulfonamides derivatives were further investigated [91].
97 Compound 71 and 72 were considered as the most active derivatives in the two
98 series of compounds with IC_{50} values for 46 and 378 nM in the inhibition of current
99 in L-929 cells model, respectively. Additionally, at the concentration of 1 μ M,
100 compound 72 displayed the most significant inhibitory effect in current in L-929
101 cells with the inhibitory ratio for 89% (Figure 14).



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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 μ M (Figure 15).



108
109

Figure 16. SAR of aryl sulfonamido tetralin derivatives.

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

112 compound **74** exhibited remarkable Kv1.5 inhibition with IC₅₀ 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**).

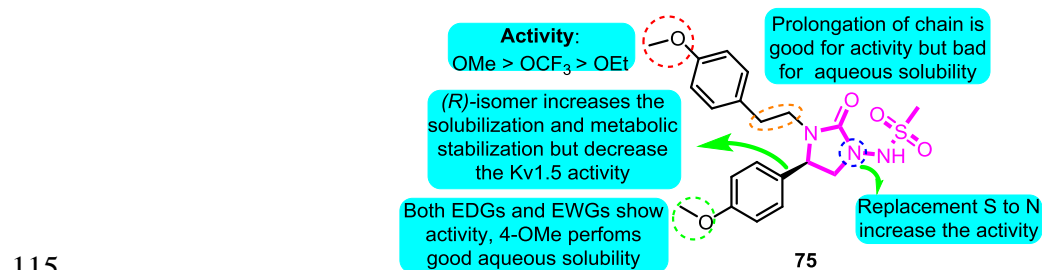


Figure 17. SAR of imidazolidinone derivatives.

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**).

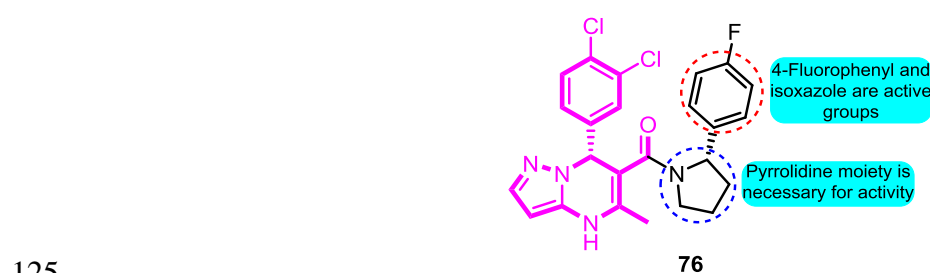
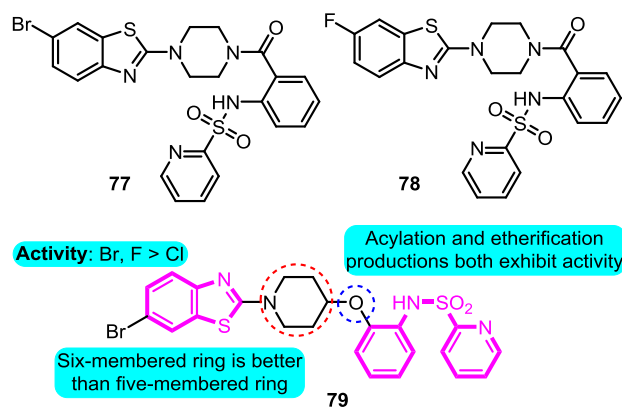


Figure 18. SAR of pyrazolodihydropyrimidines.

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 (IC₅₀: 50 nM) and very good selectivity over
 131 hERG, sodium and L-type calcium ion channels with good pharmacokinetic
 132 parameters (**Figure 18**).

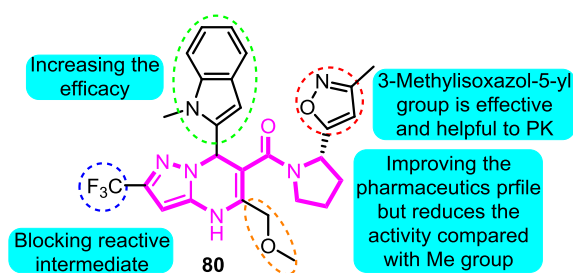


133

134

Figure 19. SAR of heteroarylsulfonamides.

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

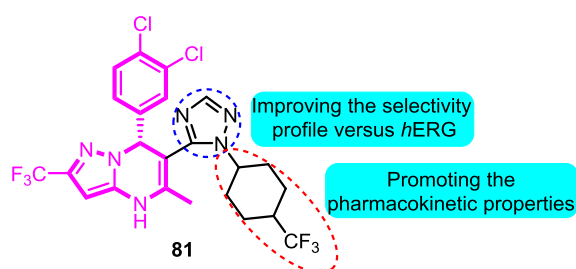


139

140

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

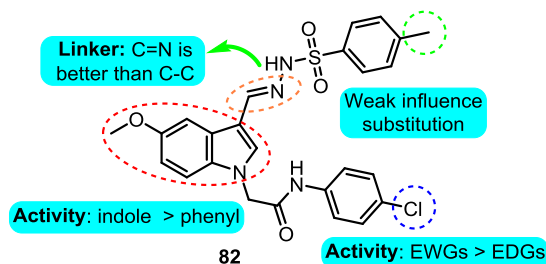
141 Finlay and colleagues [95] prepared several dihydropyrazolo[1,5-a]pyrimidine
 142 derivatives. Among the synthetic compounds, 80 showed potential to be a selective
 143 $I_{K_{ur}}$ inhibitor with Kv1.5 IC_{50} for 0.15 μ M and *h*ERG for $IC_{50} > 10 \mu$ M. Furthermore,
 144 favorable pharmacokinetic properties in rats and dogs of 80 were determined,
 145 80 was identified with less than 1% GSH adduct formation with an improved PK
 146 profile and equivalent PD efficacy to the lead compound (**Figure 20**).



147

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

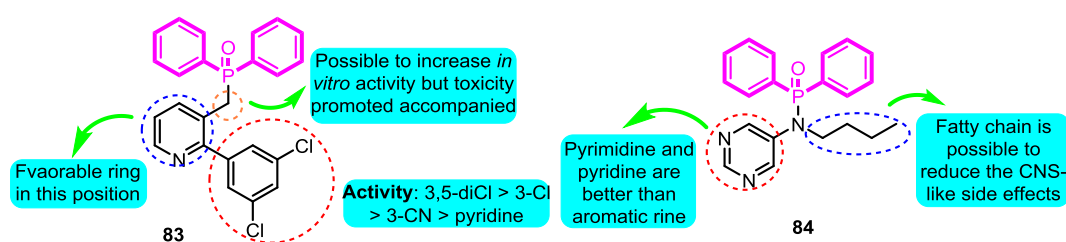
149 In 2013, triazolo and imidazo were introduced into the active scaffold
 150 dihydropyrazolopyrimidine[96]. Trifluoromethylcyclohexyl triazole analogue
 151 **81** was identified as a potent and selective Kv1.5 inhibitor (IC_{50} : 133 nM) with an
 152 acceptable PK and liability profile. Compound **81** demonstrated an improved rat
 153 PK profile and was advanced to the rat PD model (**Figure 21**).



154

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

156 With the help of pharmacophore model, Guo et al. [97] designed and
 157 synthesized a series of indole derivatives as potent Kv1.5 inhibitors. The most
 158 promising compound **82** displayed significant I_{Na} , HEK 293 $hKv1.5$ and CHO $hERG$
 159 inhibitory activities with IC_{50} values of 52.6, 0.51 and 418.35 μM , respectively,
 160 which displayed remarkable selectivity and ameliorating effects on AERP and
 161 VERP (**Figure 22**).

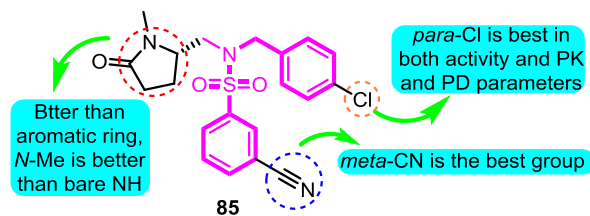


162

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

164 Olsson and co-workers [98] possessed design and pharmacological evaluation
 165 of multiple potential hits targeting on Kv1.5. The compound **83** performed best *in*
 166 *vitro* activity with Kv1.5 IC_{50} of 0.08 μM in diphenylphosphinic amide and
 167 diphenylphosphine oxide analogues (**Figure 23**). However, both $hERG$ and IKs
 168 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 IC₅₀, I_{Ks}, C_{eu20}, QT_{max} change values for 1 μM, >33%, 0.6
 171 μM, <10%, respectively.

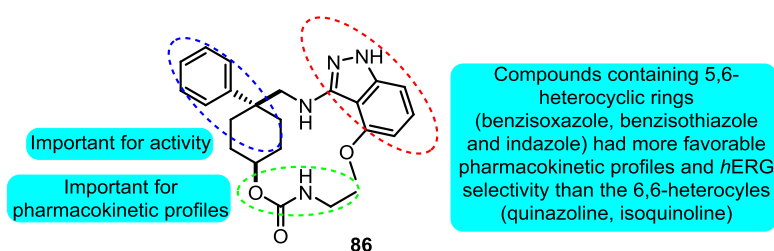


172

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 IC₅₀ value of 0.21 μM, and caused 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 IC₅₀ value from the human cellular assay. The human
 179 hERG channel was blocked by compound **85** with an IC₅₀ value of 30 μM,
 180 indicating a 140-fold margin of the hERG 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 (**Figure 24**).



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 IC₅₀: 138
 191 nM) which demonstrated significant prolongation of AERP in the rabbit

192 pharmacodynamic model(Figure 25).

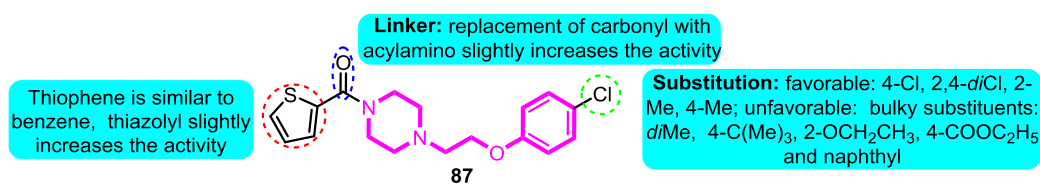


Figure 26. SAR of 1-aryloxyethyl piperazine derivatives.

195 Guo and colleagues [101] prepared a series of 1-aryloxyethyl piperazine
 196 derivatives as Kv1.5 potassium channel inhibitors. The most potent compound
 197 **87** exerted significant activity on *h*Kv1.5 (IC_{50} : 0.72 μ M), balanced Log D and
 198 permeability. In addition, comparable *in vivo* potency with sotalol and
 199 dronedarone and remarkable safety in rats of compound **87** was detected as well
 200 (Figure 26).

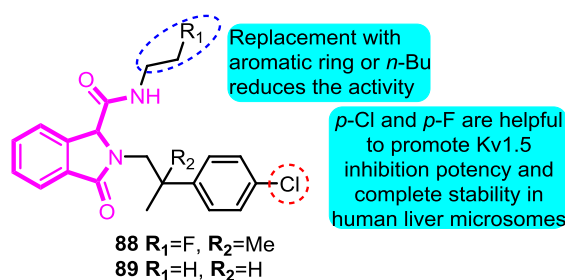


Figure 27. SAR of isoindolinones.

203 In 2016, Kajanus et al. [102] synthesized multiple isoindolinone compounds as
 204 Kv1.5 blockers. The most potent compounds **88** and **89** exhibited inhibitory effect
 205 with the IC_{50} values of 0.4 and 0.7 μ M on Kv1.5, respectively. The above mentioned
 206 two compounds were found to have desirable *in vivo* PK properties in mouse
 207 model (Figure 27).

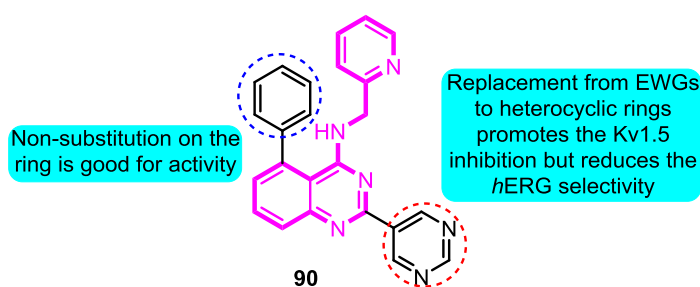


Figure 28. SAR of phenylquinazoline derivatives.

210 Finlay and co-workers [103] explored phenylquinazoline derivatives as Kv1.5
 211 inhibitors. 5-phenyl-N-(pyridin-2-ylmethyl)-2-(pyrimidin-5-yl)quinazolin-4-amine
 212 (**90**) was identified as a potent and ion channel selective inhibitor (Kv1.5 IC₅₀: 90
 213 nM, *h*ERG inhibition: 43% at 10 μM) with robust efficacy in the pre-clinical rat
 214 ventricular effective refractory period (VERP) model and the rabbit atrial effective
 215 refractory period (AERP) model (**Figure 28**).

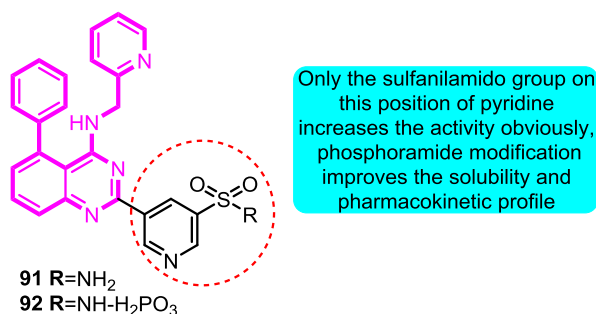


Figure 29. SAR of phenylquinazoline sulfonamide derivatives.

218 Subsequently in 2017, Gunaga et al. [58] modified the structure of **91** with a
 219 series of analogues and evaluated the *I*_{Kur} inhibitory effect.
 220 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 *h*ERG (Kv1.5 IC₅₀: 50 nM, *h*ERG IC₅₀: 1.9 μM).
 223 Compound **91** exhibited robust effects in rabbit and canine pharmacodynamic
 224 models and an acceptable cross-species pharmacokinetic profile which was then
 225 advanced as a clinical candidate. Further optimization of **91** to mitigate
 226 pH-dependent absorption resulted in identification of the corresponding
 227 phosphoramidate prodrug (**92**) with an improved solubility and pharmacokinetic
 228 profile (**Figure 29**).

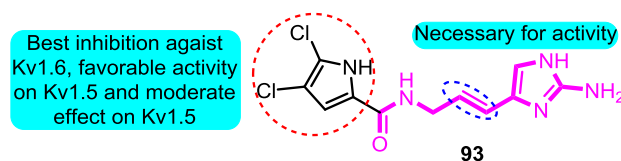


Figure 30. SAR of oroidin derivatives.

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

232 Zidar and colleagues [104] synthesized multiple derivatives as inhibitors of the
 233 voltage-gated potassium channels. The most potent inhibitor was the
 234 (*E*)-*N*-(3-(2-amino-1*H*-imidazol-4-yl)allyl)-4,5-dichloro-1*H*-pyrrole-2-carboxamide
 235 (**93**) with IC_{50} values between 1.4 and 6.1 mM against Kv1.3, Kv1.4, Kv1.5 and
 236 Kv1.6 channels (Kv1.5 IC_{50} : 6.1 μ M) (**Figure 30**).

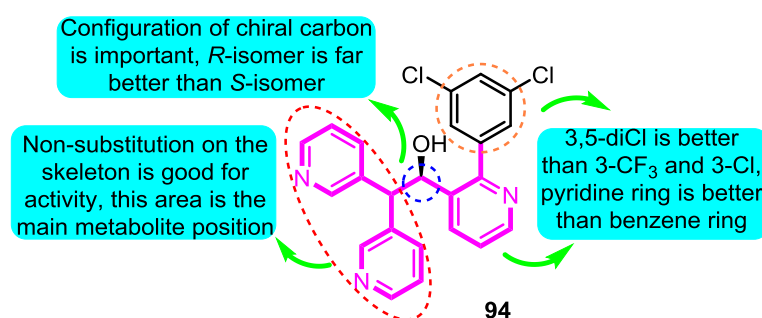


Figure 31. SAR of oroidin MK-1832.

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, I_{kur} , $I_{kr}(hERG)$ IC_{50} values for 29, 11,
 244 128000 nM, respectively, and pharmacokinetic parameters including dog *in vivo*
 245 atrial refractory period EC_{10} for 14 nM and threshold change in ventricular
 246 refractory period > 25 μ M.

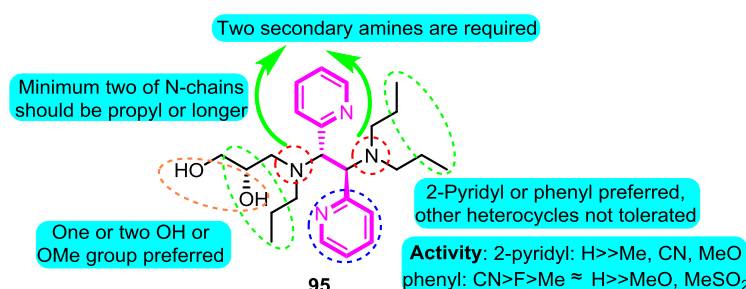
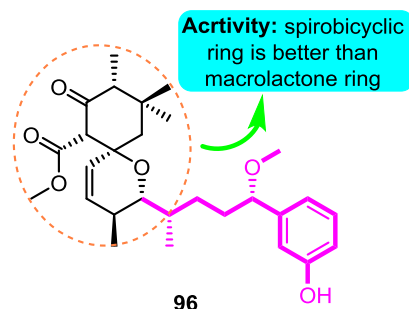


Figure 32. SAR of 1,2-bis(aryl)ethane-1,2-diamines.

249 In 2019, Kajanus and colleagues [106] prepared potassium channel blocking
 250 1,2-bis(aryl)ethane-1,2-diamines active as antiarrhythmic agents. The most
 251 promising analogue **95** displayed significant nanomolar potency in blocking Kv1.5

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



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 compound debromoaplysiatoxin 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 inhibition (IC_{50} : 0.79 μ M) 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

275 modulators aiming at Kv1.5 channel are needed in the future. Secondly, from the
276 point of application, the market of AF is relatively small, the sales condition of
277 marked anti-AF agents is not satisfactory as a whole, thus more depth
278 pharmacological investigations of roles that Kv1.5 paly are required in the future.
279 Moreover, the definite structure of Kv1.5 protein is still vacant, difficulties and
280 potential fallacy are still consisting in the design of modulators only estimating by
281 the pocket of homologous models.

282 SAR investigation is crucial for the development of novel promising clinical
283 candidates. It is anticipated that the information compiled in this review article not
284 only updates researchers with the recent reported pharmacology and SAR of Kv1.5
285 modulators, but also motivates them to design and synthesize promising Kv1.5
286 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 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 PSMCs: Human Pulmonary Arterial Smooth Muscle Cells;
- 307 *I*_{Kur} cardiac ultra-rapid delayed-rectifier;
- 308 IC₅₀:50% 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.

315 References

- 316 1. Milnes, J. T.; Madge, D. J.; Ford, J. W., New pharmacological approaches to
317 atrial fibrillation. *Drug Discov. Today* **2012**, *17*, (13-14), 654-659.
- 318 2. Amos, G. J.; Wettwer, E.; Metzger, F.; Li, Q.; Himmel, H. M.; Ravens, U.,
319 Differences between outward currents of human atrial, and subepicardial
320 ventricular myocytes. *J. Physiol.-London* **1996**, *491*, (1), 31-50.
- 321 3. Humphries, E. S. A.; Dart, C., Neuronal and cardiovascular potassium
322 channels as therapeutic drug targets: promise and pitfalls. *J. Biomol. Screen.*
323 **2015**, *20*, (9), 1055-1073.
- 324 4. Kojima, A.; Ito, Y.; Ding, W.-G.; Kitagawa, H.; Matsuura, H., Interaction of

- 325 propofol with voltage-gated human Kv1.5 channel through specific amino
326 acids within the pore region. *Eur. J. Pharmacol.* **2015**, *764*, 622-632.
- 327 5. Nerbonne, J. M.; Kass, R. S., Molecular physiology of cardiac repolarization.
328 *Physiol. Rev.* **2005**, *85*, (4), 1205-1253.
- 329 6. Tamargo, J.; Caballero, R.; Gomez, R.; Delpon, E., I-Kur/Kv1.5 channel
330 blockers for the treatment of atrial fibrillation. *Expert Opin. Inv. Drug.* **2009**,
331 *18*, (4), 399-416.
- 332 7. Yellen, G., The voltage-gated potassium channels and their relatives. *Nature*
333 **2002**, *419*, (6902), 35-42.
- 334 8. Tikhonov, D. B.; Zhorov, B. S., Homology modeling of Kv1.5 channel block
335 by cationic and electroneutral ligands. *BBA-Biomembranes* **2014**, *1838*, (3),
336 978-987.
- 337 9. Wu, J.; Ding, W. G.; Matsuura, H.; Tsuji, K.; Zang, W. J.; Horie, M., Inhibitory
338 actions of the phosphatidylinositol 3-kinase inhibitor LY294002 on the
339 human Kv1.5 channel. *Brit. J. Pharmacol.* **2009**, *156*, (2), 377-387.
- 340 10. Guex, N.; Peitsch, M. C.; Schwede, T., Automated comparative protein
341 structure modeling with SWISS-MODEL and Swiss-PdbViewer: a historical
342 perspective. *Electrophoresis* **2009**, *30* Suppl 1, S162-73.
- 343 11. Chen, R.; Chung, S.-H., Inhibition of Voltage-Gated K⁺ Channel Kv1.5 by
344 Antiarrhythmic Drugs. *Biochemistry* **2018**, *57*, (18), 2704-2710.
- 345 12. Altschul, S. F.; Madden, T. L.; Schaffer, A. A.; Zhang, J.; Zhang, Z.; Miller, W.;
346 Lipman, D. J., Gapped BLAST and PSI-BLAST: a new generation of protein
347 database search programs. *Nucleic Acids Res.* **1997**, *25*, (17), 3389-3402.
- 348 13. Robert, X.; Gouet, P., Deciphering key features in protein structures with the
349 new ENDscript server. *Nucleic Acids Res.* **2014**, *42*, (Web Server issue),
350 W320-324.
- 351 14. Tang, Y. H.; Wu, J.; Fan, T. T.; Zhang, H. H.; Gong, X. X.; Cao, Z. Y.; Zhang, J.;
352 Lin, H. W.; Han, B. N., Chemical and biological study of alysiatoxin
353 derivatives showing inhibition of potassium channel Kv1.5. *Rsc Advances*
354 **2019**, *9*, (14), 7594-7600.
- 355 15. Li, K.; Cheng, N.; Li, X. T., Inhibitory effects of cholinesterase inhibitor
356 donepezil on the Kv1.5 potassium channel. *Sci. Rep.* **2017**, *7*, 41509-41518.
- 357 16. Chen, X.; Xue, B.; Wang, J.; Liu, H.; Shi, L.; Xie, J., Potassium channels: a
358 potential therapeutic target for Parkinson's disease. *Neurosci. Bull.* **2018**, *34*,
359 (2), 341-348.
- 360 17. Li, P.; Chen, Z.; Xu, H.; Sun, H.; Li, H.; Liu, H.; Yang, H.; Gao, Z.; Jiang, H.;
361 Li, M., The gating charge pathway of an epilepsy-associated potassium
362 channel accommodates chemical ligands. *Cell Res.* **2013**, *23*, (9), 1106-1118.
- 363 18. Seifert, G.; Henneberger, C.; Steinhäuser, C., Diversity of astrocyte
364 potassium channels: An update. *Brain Res. Bull.* **2018**, *136*, 26-36.
- 365 19. Schmitt, N.; Grunnet, M.; Olesen, S. P., Cardiac potassium channel subtypes:
366 new roles in repolarization and arrhythmia. *Physiol. Rev.* **2014**, *94*, (2), 609-53.
- 367 20. Geller, J. C.; Egstrup, K.; Kulakowski, P.; Rosenqvist, M.; Jansson, M. A.;

- 368 Berggren, A.; Edvardsson, N.; Sager, P.; Crijns, H. J., Rapid conversion of
369 persistent atrial fibrillation to sinus rhythm by intravenous AZD7009. *J. Clin.*
370 *Pharmacol.* **2009**, *49*, (3), 312-322.
- 371 21. Ng, F. L.; Davis, A. J.; Jepps, T. A.; Harhun, M. I.; Yeung, S. Y.; Wan, A.;
372 Reddy, M.; Melville, D.; Nardi, A.; Khong, T. K.; Greenwood, I. A.,
373 Expression and function of the K plus channel KCNQ genes in human
374 arteries. *Br. J. Pharmacol.* **2011**, *162*, (1), 42-53.
- 375 22. Barros, F.; Pardo, L. A.; Dominguez, P.; Maria Sierra, L.; de la Pena, P., New
376 Structures and Gating of Voltage-Dependent Potassium (Kv) Channels and
377 Their Relatives: A Multi-Domain and Dynamic Question. *Int. J. Mol. Sci.*
378 **2019**, *20*, (2).
- 379 23. Mozrzymas, J. W.; Teisseyre, A.; Vittur, F., Propofol blocks voltage-gated
380 potassium channels in human T lymphocytes. *Biochem. Pharmacol.* **1996**, *52*,
381 (6), 843-9.
- 382 24. Teisseyre, A.; Michalak, K., Inhibition of the activity of human lymphocyte
383 Kv1.3 potassium channels by resveratrol. *J. Membr. Biol.* **2006**, *214*, (3),
384 123-129.
- 385 25. Ishii, T.; Warabi, E.; Siow, R. C. M.; Mann, G. E., Sequestosome1/p62: A
386 regulator of redox-sensitive voltage-activated potassium channels, arterial
387 remodeling, inflammation, and neurite outgrowth. *Free Radic. Biol. Med.*
388 **2013**, *65*, 102-116.
- 389 26. dos Santos-Nascimento, T.; Veras, K. M.; Cruz, J. S.; Leal-Cardoso, J. H.,
390 Inhibitory Effect of Terpinen-4-ol on Voltage-Dependent Potassium Currents
391 in Rat Small Sensory Neurons. *J. Nat. Prod.* **2015**, *78*, (2), 173-180.
- 392 27. Kulcitki, V.; Harghel, P.; Ungur, N., Unusual cyclic terpenoids with terminal
393 pendant prenyl moieties: from occurrence to synthesis. *Nat. Prod. Rep.* **2014**,
394 *31*, (12), 1686-1720.
- 395 28. Menezes, P. M. N.; Brito, M. C.; de Paiva, G. O.; dos Santos, C. O.; de
396 Oliveira, L. M.; Ribeiro, L. A. D.; de Lima, J. T.; Lucchese, A. M.; Silva, F. S.,
397 Relaxant effect of *Lippia origanoides* essential oil in guinea-pig trachea
398 smooth muscle involves potassium channels and soluble guanylyl cyclase. *J.*
399 *Ethnopharmacol.* **2018**, *220*, 16-25.
- 400 29. Kalyaanamoorthy, S.; Barakat, K. H., Development of safe crugs: the *hERG*
401 challenge. *Med. Res. Rev.* **2018**, *38*, (2), 525-555.
- 402 30. Cheong, A.; Dedman, A. M.; Beech, D. J., Expression and function of native
403 potassium channel (K-v alpha 1) subunits in terminal arterioles of rabbit. *J.*
404 *Physiol.-London* **2001**, *534*, (3), 691-700.
- 405 31. Xie, Y.; Ding, W.; Liu, Y.; Yu, M.; Sun, X.; Matsuura, H., Long-term 4-AP
406 treatment facilitates functional expression of human Kv1.5 channel. *Eur. J.*
407 *Pharmacol.* **2019**, *844*, 195-203.
- 408 32. Eldstrom, J.; Wang, Z.; Xu, H.; Pourrier, M.; Ezrin, A.; Gibson, K.; Fedida, D.,
409 The molecular basis of high-affinity binding of the antiarrhythmic
410 compound vernakalant (RSD1235) to Kv1.5 channels. *Mol. Pharmacol.* **2007**,

- 411 72, (6), 1522-1534.
- 412 33. Kodama, I.; Kamiya, K.; Honjo, H.; Toyama, J., Acute and chronic effects of
413 amiodarone on mammalian ventricular cells. *Jpn. Heart J.* **1996**, *37*, (5),
414 719-730.
- 415 34. Herrera, D.; Mamarbachi, A.; Simoes, M.; Parent, L.; Sauve, R.; Wang, Z. G.;
416 Nattel, S., A single residue in the S6 transmembrane domain governs the
417 differential flecainide sensitivity of voltage-gated potassium channels. *Mol.*
418 *Pharmacol.* **2005**, *68*, (2), 305-316.
- 419 35. Lin, S.; Wang, Z.; Fedida, D., Influence of permeating ions on Kv1.5 channel
420 block by nifedipine. *Am. J. Physiol-Heart C.* **2001**, *280*, (3), H1160-H1172.
- 421 36. Franqueza, L.; Valenzuela, C.; Delpon, E.; Longobardo, M.; Caballero, R.;
422 Tamargo, J., Effects of propafenone and 5-hydroxy-propafenone on hKv1.5
423 channels. *Brit. J. Pharmacol.* **1998**, *125*, (5), 969-978.
- 424 37. Fedida, D., Gating charge and ionic currents associated with quinidine block
425 of human Kv1.5 delayed rectifier channels. *The Journal of physiology* **1997**, *499*
426 (Pt 3), 661-675.
- 427 38. Caballero, R.; Gomez, R.; Nunez, L.; Moreno, I.; Tamargo, J.; Delpon, E.,
428 Diltiazem inhibits hKv1.5 and Kv4.3 currents at therapeutic concentrations.
429 *Cardiovasc. Res.* **2004**, *64*, (3), 457-466.
- 430 39. Chow, L. W. C.; Cheng, K.-S.; Wong, K.-L.; Leung, Y.-M., Voltage-gated K+
431 channels promote BT-474 breast cancer cell migration. *Chinese J. Cancer Res.*
432 **2018**, *30*, (6), 613-622.
- 433 40. Malayev, A. A.; Nelson, D. J.; Philipson, L. H., Mechanism of clofilium block
434 of the human Kv1.5 delayed rectifier potassium channel. *Mol. Pharmacol.*
435 **1995**, *47*, (1), 198-205.
- 436 41. Yang, I. C. H.; Scherz, M. W.; Bahinski, A.; Bennett, P. B.; Murray, K. T.,
437 Stereoselective interactions of the enantiomers of chromanol 293B with
438 human voltage-gated potassium channels. *J. Pharmacol. Exp. Ther.* **2000**, *294*,
439 (3), 955-962.
- 440 42. Kobayashi, S.; Reien, Y.; Ogura, T.; Saito, T.; Masuda, Y.; Nakaya, H.,
441 Inhibitory effect of bepridil on hKv1.5 channel current: comparison with
442 amiodarone and E-4031. *Eur. J. Pharmacol.* **2001**, *430*, (2-3), 149-157.
- 443 43. Lee, H. M.; Hahn, S. J.; Choi, B. H., Blockade of Kv1.5 by paroxetine, an
444 antidepressant drug. *Korean J. Physiol. Pha.* **2016**, *20*, (1), 75-82.
- 445 44. Dai, F. F.; Mao, Z. F.; Xia, J.; Zhu, S. P.; Wu, Z. Y., Fluoxetine protects against
446 big endothelin-1 induced anti-apoptosis by rescuing Kv1.5 channels in
447 human pulmonary arterial smooth muscle cells. *Yonsei Med. J.* **2012**, *53*, (4),
448 842-848.
- 449 45. Lee, H. M.; Hahn, S. J.; Choi, B. H., Blockade of Kv1.5 channels by the
450 antidepressant drug sertraline. *Korean J. Physiol. Pha.* **2016**, *20*, (2), 193-200.
- 451 46. Yu, J.; Park, M.-H.; Jo, S.-H., Inhibitory effects of cortisone and
452 hydrocortisone on human Kv1.5 channel currents. *Eur. J. Pharmacol.* **2015**,
453 *746*, 158-166.

- 454 47. Lammers, C.; Dartsch, T.; Brandt, M. C.; Rottlander, D.; Halbach, M.;
455 Peinkofer, G.; Ockenpoehler, S.; Weiergraeber, M.; Schneider, T.; Reuter, H.;
456 Muller-Ehmsen, J.; Hescheler, J.; Hoppe, U. C.; Zobel, C., Spironolactone
457 prevents aldosterone induced increased duration of atrial fibrillation in rat.
458 *Cell Physiol. Biochem.* **2012**, *29*, (5-6), 833-840.
- 459 48. Frolov, R. V.; Singh, S., Celecoxib and ion channels: A story of unexpected
460 discoveries. *Eur. J. Pharmacol.* **2014**, *730*, 61-71.
- 461 49. Luzhkov, V. B.; Nilsson, J.; Arhem, P.; Aqvist, J., Computational modelling of
462 the open-state K(v)1.5 ion channel block by bupivacaine. *BBA-Proteins*
463 *Proteom.* **2003**, *1652*, (1), 35-51.
- 464 50. Valenzuela, C.; Delpon, E.; Tamkun, M. M.; Tamargo, J.; Snyders, D. J.,
465 Stereoselective block of a human cardiac potassium channel (Kv1.5) by
466 bupivacaine enantiomers. *Biophys. J.* **1995**, *69*, (2), 418-427.
- 467 51. Vonderlin, N.; Fischer, F.; Zitron, E.; Seyler, C.; Scherer, D.; Thomas, D.;
468 Katus, H. A.; Scholz, E. P., Inhibition of cardiac Kv1.5 potassium current by
469 the anesthetic midazolam: mode of action. *Drug Des. Dev. Ther.* **2014**, *8*,
470 2263-2271.
- 471 52. Su, J. P.; Huang, Y.; Lenka, N.; Hescheler, J.; Ullrich, S., The expression and
472 regulation of depolarization-activated K⁺ channels in the insulin-secreting
473 cell line INS-1. *Pflug. Arch.-Eur. J. Phy.* **2001**, *442*, (1), 49-56.
- 474 53. Caballero, R.; Moreno, I.; Gonzalez, T.; Valenzuela, C.; Tamargo, J.; Delpon,
475 E., Putative binding sites for benzocaine on a human cardiac cloned channel
476 (Kv1.5). *Cardiovasc. Res.* **2002**, *56*, (1), 104-117.
- 477 54. Jie, L.; Wu, W.; Li, G.; Xiao, G.; Zhang, S.; Li, G.; Wang, Y., Clemizole
478 hydrochloride blocks cardiac potassium currents stably expressed in HEK
479 293 cells. *Brit. J. Pharmacol.* **2017**, *174*, (3), 254-266.
- 480 55. Wirth, K. J.; Brendel, J.; Steinmeyer, K.; Linz, D. K.; Ruetten, H.; Goegelein,
481 H., *In vitro* and *in vivo* effects of the atrial selective antiarrhythmic
482 compound AVE1231. *J. Cardiovasc. Pharmacol.* **2007**, *49*, (4), 197-206.
- 483 56. Persson, F.; Carlsson, L.; Duke, G.; Jacobson, I., Blocking characteristics of
484 hKv1.5 and hKv4.3/hKChIP2.2 after administration of the novel
485 antiarrhythmic compound AZD7009. *J. Cardiovasc. Pharmacol.* **2005**, *46*, (1),
486 7-17.
- 487 57. Lloyd, J.; Finlay, H. J.; Vacarro, W.; Hyunh, T.; Kover, A.; Bhandaru, R.; Yan,
488 L.; Atwal, K.; Conder, M. L.; Jenkins-West, T.; Shi, H.; Huang, C.; Li, D.; Sun,
489 H.; Levesque, P., Pyrrolidine amides of pyrazolodihydropyrimidines as
490 potent and selective KV1.5 blockers. *Bioorg. Med. Chem. Lett.* **2010**, *20*, (4),
491 1436-1439.
- 492 58. Gunaga, P.; Lloyd, J.; Mummadi, S.; Banerjee, A.; Dhondi, N. K.; Hennan, J.;
493 Subray, V.; Jayaram, R.; Rajugowda, N.; Reddy, K. U.; Kumaraguru, D.;
494 Mandal, U.; Beldona, D.; Adisechen, A. K.; Yadav, N.; Warriar, J.; Johnson, J.
495 A.; Sale, H.; Putlue, S. P.; Saxena, A.; Chimalakonda, A.; Mandlekar, S.;
496 Conder, M.; Xing, D.; Gupta, A. K.; Gupta, A.; Rampulla, R.; Mathur, A.;

- 497 Levesque, P.; Wexler, R. R.; Finlay, H. J., Selective I-Kur inhibitors for the
498 potential treatment of atrial fibrillation: optimization of the phenyl
499 quinazoline series leading to clinical candidate 5-
500 5-phenyl-4-(pyridin-2-ylmethylamino)quinazolin-2-yl pyridine-3-sulfon
501 amide. *J. Med. Chem.* **2017**, *60*, (9), 3795-3803.
- 502 59. Loose, S.; Mueller, J.; Wettwer, E.; Knaut, M.; Ford, J.; Milnes, J.; Ravens, U.,
503 Effects of IKur blocker MK-0448 on human right atrial action potentials
504 from patients in sinus rhythm and in permanent atrial fibrillation. *Front.*
505 *Pharmacol.* **2014**, *5*, 26-32.
- 506 60. Ford, J.; Milnes, J.; El Haou, S.; Wettwer, E.; Loose, S.; Matschke, K.; Tyl, B.;
507 Round, P.; Ravens, U., The positive frequency-dependent
508 electrophysiological effects of the IKur inhibitor XEN-D0103 are desirable
509 for the treatment of atrial fibrillation. *Heart Rhythm* **2016**, *13*, (2), 555-564.
- 510 61. Gautier, P.; Guillemare, E.; Djandjighian, L.; Marion, A.; Planchenault, J.;
511 Bernhart, C.; Herbert, J. M.; Nisato, D., *In vivo* and *in vitro* characterization of
512 the novel antiarrhythmic agent SSR149744C - Electrophysiological,
513 anti-adrenergic, and anti-angiotensin II effects. *J. Cardiovasc. Pharmacol.* **2004**,
514 *44*, (2), 244-257.
- 515 62. Gasparoli, L.; D'Amico, M.; Masselli, M.; Pillozzi, S.; Caves, R.; Khuwaileh,
516 R.; Tiedke, W.; Mugridge, K.; Pratesi, A.; Mitcheson, J. S.; Basso, G.;
517 Becchetti, A.; Arcangeli, A., New pyrimido-indole compound CD-160130
518 preferentially inhibits the K(V)11.1B isoform and produces antileukemic
519 effects without cardiotoxicity. *Mol. Pharmacol.* **2015**, *87*, (2), 183-196.
- 520 63. Han, B.; Liang, T.; Keen, L. J.; Fan, T.; Zhang, X.; Xu, L.; Zhao, Q.; Wang, S.;
521 Lin, H., Two marine cyanobacterial aplysiatoxin polyketides,
522 neo-debromoaplysiatoxin A and B, with K⁺ channel inhibition activity. *Org.*
523 *Lett.* **2018**, *20*, (3), 578-581.
- 524 64. Grissmer, S.; Nguyen, A. N.; Aiyar, J.; Hanson, D. C.; Mather, R. J.; Gutman,
525 G. A.; Karmilowicz, M. J.; Auperin, D. D.; Chandy, K. G., Pharmacological
526 characterization of five cloned voltage-gated K⁺ channels, types Kv1.1, 1.2,
527 1.3, 1.5, and 3.1, stably expressed in mammalian cell lines. *Mol. Pharmacol.*
528 **1994**, *45*, (6), 1227-1234.
- 529 65. Kwak, Y. G.; Kim, D. K.; Ma, T.; Park, S.-A.; Park, H.; Jung, Y. H.; Yoo, D.-J.;
530 Eun, J. S., Torilin from *Torilis japonica* (Houtt.) DC. blocks hKv1.5 channel
531 current. *Arch. Pharm. Res.* **2006**, *29*, (10), 834-839.
- 532 66. Jin, S.; Guo, Q.; Xu, J.; Yu, P.; Liu, J.; Tang, Y., Antiarrhythmic ionic
533 mechanism of Guanfu base A -Selective inhibition of late sodium current in
534 isolated ventricular myocytes from guinea pigs. *Chinese J. Nat. Medicines*
535 **2015**, *13*, (5), 361-367.
- 536 67. Jeong, I.; Choi, B. H.; Hahn, S. J., Effects of lobeline, a nicotinic receptor
537 ligand, on the cloned Kv1.5. *Pflug. Arch.-Eur. J. Phy.* **2010**, *460*, (5), 851-862.
- 538 68. Fischer, F.; Vonderlin, N.; Zitron, E.; Seyler, C.; Scherer, D.; Becker, R.; Katus,
539 H. A.; Scholz, E. P., Inhibition of cardiac Kv1.5 and Kv4.3 potassium

- 540 channels by the class Ia anti-arrhythmic ajmaline: mode of action. *N.-S. Arch.*
541 *Pharmacol.* **2013**, *386*, (11), 991-999.
- 542 69. Choe, H.; Lee, Y. K.; Lee, Y. T.; Choe, H.; Ko, S. H.; Joo, C. U.; Kim, M. H.;
543 Kim, G. S.; Eun, J. S.; Kim, J. H.; Chae, S. W.; Kwak, Y. G., Papaverine blocks
544 hKv1.5 channel current and human atrial ultrarapid delayed rectifier K⁺
545 currents. *Can. J. Cardiol.* **2003**, *304*, (2), 706-712.
- 546 70. Li, K.; Pi, M.; Li, X., The inhibitory effects of *levo*-tetrahydropalmatine on rat
547 Kv1.5 channels expressed in HEK293 cells. *Eur. J. Pharmacol.* **2017**, *809*,
548 105-110.
- 549 71. Li, Y. F.; Tu, D. N.; Xiao, H.; Du, Y. M.; Zou, A. R.; Liao, Y. H.; Dong, S. H.,
550 Aconitine blocks HERG and Kv1.5 potassium channels. *J. Ethnopharmacol.*
551 **2010**, *131*, (1), 187-195.
- 552 72. Ou, X.; Bin, X.; Wang, L.; Li, M.; Yang, Y.; Fan, X.; Zeng, X., Myricetin
553 inhibits K(v)1.5 channels in HEK293 cells. *Mol. Med. Rep.* **2016**, *13*, (2),
554 1725-1731.
- 555 73. Liu, Y.; Xu, X.; Liu, Z.; Du, X.; Chen, K.; Xin, X.; Jin, Z.; Shen, J.; Hu, Y.; Li, G.;
556 Jin, M., Effects of the natural flavone trimethylapigenin on cardiac
557 potassium currents. *Biochem. Pharmacol.* **2012**, *84*, (4), 498-506.
- 558 74. Yang, L.; Ma, J.; Zhang, P.; Zou, A.; Tu, D., Quercetin activates human Kv1.5
559 channels by a residue I502 in the S6 segment *Clin. Exp. Pharmacol. P.* **2009**, *36*,
560 (2), 154-161.
- 561 75. Wu, H.-J.; Wu, W.; Sun, H.-Y.; Qin, G.-W.; Wang, H.-B.; Wang, P.;
562 Yalamanchili, H. K.; Wang, J.; Tse, H.-F.; Lau, C.-P.; Vanhoutte, P. M.; Li,
563 G.-R., Acacetin causes a frequency- and use-dependent blockade of hKv1.5
564 channels by binding to the S6 domain. *J. Mol. Cell. Cardiol.* **2011**, *51*, (6),
565 966-973.
- 566 76. Paffett, M. L.; Lucas, S. N.; Campen, M. J., Resveratrol reverses
567 monocrotaline-induced pulmonary vascular and cardiac dysfunction: A
568 potential role for atrogen-1 in smooth muscle. *Vasc. Pharmacol.* **2012**, *56*, (1-2),
569 64-73.
- 570 77. Kwak, Y. G.; Choi, B.-H.; Kim, D. K.; Eun, J. S., Decursin from *Angelica gigas*
571 Nakai blocks hKv1.5 channel. *Biomol. Ther.* **2011**, *19*, (1), 33-37.
- 572 78. Karczewski, J.; Kiss, L.; Kane, S. A.; Koblan, K. S.; Lynch, R. J.; Spencer, R.
573 H., High-throughput analysis of drug binding interactions for the human
574 cardiac channel, Kv1.5. *Biochem. Pharmacol.* **2009**, *77*, (2), 177-185.
- 575 79. Yang, Q.; Lv, Q.; Feng, M.; Liu, M.; Feng, Y.; Lin, S.; Yang, J.; Hu, J., Taurine
576 prevents the electrical remodeling in ach-CaCl₂ induced atrial fibrillation in
577 rats. In *Taurine 10*, Lee, D. H.; Schaffer, S. W.; Park, E.; Kim, H. W., Eds. 2017;
578 Vol. 975, pp 821-830.
- 579 80. Peukert, S.; Brendel, J.; Pirard, B.; Bruggemann, A.; Below, P.; Kleemann, H.
580 W.; Hemmerle, H.; Schmidt, W., Identification, synthesis, and activity of
581 novel blockers of the voltage-gated potassium channel Kv1.5. *J. Med. Chem.*
582 **2003**, *46*, (4), 486-498.

- 583 81. Peukert, S.; Brendel, J.; Pirard, B.; Strubing, C.; Kleemann, H. W.; Bohme, T.;
584 Hemmerle, H., Pharmacophore-based search, synthesis, and biological
585 evaluation of anthranilic amides as novel blockers of the Kv1.5 channel.
586 *Bioorg. Med. Chem. Lett.* **2004**, *14*, (11), 2823-2827.
- 587 82. Schmitz, A.; Sankaranarayanan, A.; Azam, P.; Schmidt-Lassen, K.; Homerick,
588 D.; Hansel, W.; Wulff, H., Design of PAP-1, a selective small molecule Kv1.3
589 blocker, for the suppression of effector memory T cells in autoimmune
590 diseases. *Mol. Pharmacol.* **2005**, *68*, (5), 1254-1270.
- 591 83. Blass, B. E.; Coburn, K.; Lee, W.; Fairweather, N.; Fluxe, A.; Wu, S.; Janusz, J.
592 M.; Murawsky, M.; Fadayel, G. M.; Fang, B.; Hare, M.; Ridgeway, J.; White,
593 R.; Jackson, C.; Djandjighian, L.; Hedges, R.; Wireko, F. C.; Ritter, A. L.,
594 Synthesis and evaluation of
595 (2-phenethyl-2H-1,2,3-triazol-4-yl)(phenyl)methanones as Kv1.5 channel
596 blockers for the treatment of atrial fibrillation. *Bioorg. Med. Chem. Lett.* **2006**,
597 *16*, (17), 4629-4632.
- 598 84. Fluxe, A.; Wu, S. D.; Sheffer, J. B.; Janusz, J. M.; Murawsky, M.; Fadayel, G.
599 M.; Fang, B.; Hare, M.; Djandjighian, L., Discovery and synthesis of
600 tetrahydroindolone-derived carbamates as Kv1.5 blockers. *Bioorg. Med.*
601 *Chem. Lett.* **2006**, *16*, (22), 5855-5858.
- 602 85. Wu, S.; Fluxe, A.; Janusz, J. M.; Sheffer, J. B.; Browning, G.; Blass, B.; Coburn,
603 K.; Hedges, R.; Murawsky, M.; Fang, B.; Fadayel, G. M.; Hare, M.;
604 Djandjighian, L., Discovery and synthesis of tetrahydroindolone derived
605 semicarbazones as selective Kv1.5 blockers. *Bioorg. Med. Chem. Lett.* **2006**, *16*,
606 (22), 5859-5863.
- 607 86. Nanda, K. K.; Nolt, M. B.; Cato, M. J.; Kane, S. A.; Kiss, L.; Spencer, R. H.;
608 Wang, J.; Lynch, J. J.; Regan, C. P.; Stump, G. L.; Li, B.; White, R.; Yeh, S.;
609 Bogusky, M. J.; Bilodeau, M. T.; Dinsmore, C. J.; Lindsley, C. W.; Hartman, G.
610 D.; Wolkenberg, S. E.; Trotter, B. W., Potent antagonists of the Kv1.5
611 potassium channel: Synthesis and evaluation of analogous
612 *N,N*-diisopropyl-2-(pyridine-3-yl)acetamides. *Bioorg. Med. Chem. Lett.* **2006**,
613 *16*, (22), 5897-5901.
- 614 87. Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G.
615 L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.;
616 Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G.
617 D.; Dinsmore, C. J., Design and synthesis of novel isoquinoline-3-nitriles as
618 orally bioavailable Kv1.5 antagonists for the treatment of atrial fibrillation. *J.*
619 *Med. Chem.* **2006**, *49*, (24), 6954-6957.
- 620 88. Eun, J. S.; Kim, K. S.; Kim, H. N.; Park, S. A.; Ma, T.-Z.; Lee, K. A.; Kim, D. K.;
621 Kim, H. K.; Kim, I. S.; Jung, Y. H.; Zee, O. P.; Yoo, D. J.; Kwak, Y. G.,
622 Synthesis of psoralen derivatives and their blocking effect of *h*Kv1.5
623 channel. *Arch. Pharm. Res.* **2007**, *30*, (2), 155-160.
- 624 89. Jackson, C. M.; Blass, B.; Coburn, K.; Djandjighian, L.; Fadayel, G.; Fluxe, A.
625 J.; Hodson, S. J.; Janusz, J. M.; Murawsky, M.; Ridgeway, J. M.; White, R. E.;

- 626 Wu, S., Evolution of thiazolidine-based blockers of human Kv1.5 for the
627 treatment of atrial arrhythmias. *Bioorg. Med. Chem. Lett.* **2007**, *17*, (1), 282-284.
- 628 90. Lloyd, J.; Atwal, K. S.; Finlay, H. J.; Nyman, M.; Huynh, T.; Bhandaru, R.;
629 Kover, A.; Schmidt, J.; Vaccaro, W.; Conder, M. L.; Jenkins-West, T.;
630 Levesque, P., Benzopyran sulfonamides as K(v)1.5 potassium channel
631 blockers. *Bioorg. Med. Chem. Lett.* **2007**, *17*, (12), 3271-3275.
- 632 91. Finlay, H. J.; Lloyd, J.; Nyman, M.; Conder, M. L.; West, T.; Levesque, P.;
633 Atwal, K., Pyrano- [2,3b] -pyridines as potassium channel antagonists.
634 *Bioorg. Med. Chem. Lett.* **2008**, *18*, (8), 2714-2718.
- 635 92. Gross, M. F.; Castle, N. A.; Zou, A.; Wickenden, A. D.; Yu, W.; Spear, K. L.,
636 Aryl sulfonamido tetralin inhibitors of the Kv1.5 ion channel. *Bioorg. Med.*
637 *Chem. Lett.* **2009**, *19*, (11), 3063-3066.
- 638 93. Blass, B. E.; Fensome, A.; Trybulski, E.; Magolda, R.; Gardell, S. J.; Liu, K.;
639 Samuel, M.; Feingold, I.; Huselton, C.; Jackson, C. M.; Djandjighian, L.; Ho,
640 D.; Hennan, J.; Janusz, J. M., Selective Kv1.5 blockers: Development of
641 (R)-1-(methylsulfonylamino)-3- 2-(4-methoxyphenyl)ethyl -4-(4-methoxyphe
642 nyl)-2-imidazolidinone (KVI-020/WYE-160020) as a potential treatment for
643 atrial arrhythmia. *J. Med. Chem.* **2009**, *52*, (21), 6531-6534.
- 644 94. Blass, B., Derivatives of heteroarylsulfonamides, their preparation, and their
645 application in human therapy patent highlight. *ACS Med. Chem. Lett.* **2012**, *3*,
646 (8), 618-619.
- 647 95. Finlay, H. J.; Lloyd, J.; Vaccaro, W.; Kover, A.; Yan, L.; Bhav, G.; Prol, J.;
648 Tram, H.; Bhandaru, R.; Caringal, Y.; DiMarco, J.; Gan, J.; Harper, T.; Huang,
649 C.; Conder, M. L.; Sun, H.; Levesque, P.; Blonar, M.; Atwal, K.; Wexler, R.,
650 Discovery of
651 ((S)-5-(methoxymethyl)-7-(1-methyl-1H-indol-2-yl)-2-(trifluoromethyl)-4,
652 7-dihydropyrazolo 1,5-a pyrimidin-6-yl)((S)-2-(3-methylisoxazol-5-yl)pyr
653 rolidin-1-yl)methanone as a potent and selective I-Kur inhibitor. *J. Med.*
654 *Chem.* **2012**, *55*, (7), 3036-3048.
- 655 96. Finlay, H. J.; Jiang, J.; Caringal, Y.; Kover, A.; Conder, M. L.; Xing, D.;
656 Levesque, P.; Harper, T.; Hsueh, M. M.; Atwal, K.; Blonar, M.; Wexler, R.;
657 Lloyd, J., Triazolo and imidazo dihydropyrazolopyrimidine potassium
658 channel antagonists. *Bioorg. Med. Chem. Lett.* **2013**, *23*, (6), 1743-1747.
- 659 97. Guo, X.; Yang, Q.; Xu, J.; Zhang, L.; Chu, H.; Yu, P.; Zhu, Y.; Wei, J.; Chen, W.;
660 Zhang, Y.; Zhang, X.; Sun, H.; Tang, Y.; You, Q., Design and bio-evaluation
661 of indole derivatives as potent Kv1.5 inhibitors. *Bioorg. Med. Chem.* **2013**, *21*,
662 (21), 6466-6476.
- 663 98. Olsson, R. I.; Jacobson, I.; Bostrom, J.; Fex, T.; Bjore, A.; Olsson, C.; Sundell,
664 J.; Gran, U.; Ohrn, A.; Nordin, A.; Gyll, J.; Thorstensson, M.; Hayen, A.;
665 Aplaner, K.; Hidestal, O.; Jiang, F.; Linhardt, G.; Forsstrom, E.; Collins, T.;
666 Sundqvist, M.; Lindhardt, E.; Astrand, A.; Lofberg, B., Synthesis and
667 evaluation of diphenylphosphinic amides and diphenylphosphine oxides as
668 inhibitors of Kv1.5. *Bioorg. Med. Chem. Lett.* **2013**, *23*, (3), 706-710.

- 669 99. Olsson, R. I.; Jacobson, I.; Iliefski, T.; Bostrom, J.; Davidsson, O.; Fjellstrom,
670 O.; Bjore, A.; Olsson, C.; Sundell, J.; Gran, U.; Gyll, J.; Malmberg, J.; Hidestål,
671 O.; Emtenas, H.; Svensson, T.; Yuan, Z. Q.; Strandlund, G.; Astrand, A.;
672 Lindhardt, E.; Linhardt, G.; Forsstrom, E.; Hogberg, A.; Persson, F.;
673 Andersson, B.; Ronnberg, A.; Lofberg, B., Lactam sulfonamides as potent
674 inhibitors of the Kv1.5 potassium ion channel. *Bioorg. Med. Chem. Lett.* **2014**,
675 *24*, (5), 1269-1273.
- 676 100. Johnson, J. A.; Xu, N.; Jeon, Y.; Finlay, H. J.; Kover, A.; Conder, M. L.; Sun,
677 H.; Li, D.; Levesque, P.; Hsueh, M.-M.; Harper, T. W.; Wexler, R. R.; Lloyd, J.,
678 Design, synthesis and evaluation of phenethylaminoheterocycles as K(v)1.5
679 inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, (14), 3018-3022.
- 680 101. Guo, X.; Ma, X.; Yang, Q.; Xu, J.; Huang, L.; Jia, J.; Shan, J.; Liu, L.; Chen, W.;
681 Chu, H.; Wei, J.; Zhang, X.; Sun, H.; Tang, Y.; You, Q., Discovery of
682 1-aryloxyethyl piperazine derivatives as Kv1.5 potassium channel inhibitors
683 (part I). *Eur. J. Med. Chem.* **2014**, *81*, 89-94.
- 684 102. Kajanus, J.; Jacobson, I.; Astrand, A.; Olsson, R. I.; Gran, U.; Bjore, A.;
685 Fjellstrom, O.; Davidsson, O.; Emtenas, H.; Dahlen, A.; Lofberg, B.; Yuan, Z.;
686 Sundell, J.; Cassel, J.; Gyll, J.; Iliefski, T.; Hogberg, A.; Lindhardt, E.;
687 Malmberg, J., Isoindolinone compounds active as Kv1.5 blockers identified
688 using a multicomponent reaction approach. *Bioorg. Med. Chem. Lett.* **2016**, *26*,
689 (8), 2023-2029.
- 690 103. Finlay, H. J.; Johnson, J. A.; Lloyd, J. L.; Jiang, J.; Neels, J.; Gunaga, P.;
691 Banerjee, A.; Dhondi, N.; Chimalakonda, A.; Mandlekar, S.; Conder, M. L.;
692 Sale, H.; Xing, D.; Levesque, P.; Wexler, R. R., Discovery of
693 5-Phenyl-N-(pyridin-2-ylmethyl)-2-(pyrimidin-5-yl)quinazolin-4-amine as a
694 Potent I-Kur Inhibitor. *ACS Med. Chem. Lett.* **2016**, *7*, (9), 831-834.
- 695 104. Zidar, N.; Zula, A.; Tomasic, T.; Rogers, M.; Kirby, R. W.; Tytgat, J.; Peigneur,
696 S.; Kikelj, D.; Ilas, J.; Masic, L. P., Clathrocin, hymenidin and oroidin, and
697 their synthetic analogues as inhibitors of the voltage-gated potassium
698 channels. *Eur. J. Med. Chem.* **2017**, *139*, 232-241.
- 699 105. Wolkenberg, S. E.; Nolt, M. B.; Bilodeau, M. T.; Trotter, B. W.; Manley, P. J.;
700 Kett, N. R.; Nanda, K. K.; Wu, Z. C.; Cato, M. J.; Kane, S. A.; Kiss, L.;
701 Spencer, R. H.; Wang, J. X.; Lynch, J. J.; Regan, C. P.; Stump, G. L.; Li, B.;
702 White, R.; Yeh, S. Z.; Dinsmore, C. J.; Lindsley, C. W.; Hartman, G. D.,
703 Discovery of MK-1832, a Kv1.5 inhibitor with improved selectivity and
704 pharmacokinetics. *Bioorg. Med. Chem. Lett.* **2017**, *27*, (4), 1062-1069.
- 705 106. Kajanus, J.; Antonsson, T.; Carlsson, L.; Jurva, U.; Pettersen, A.; Sundell, J.;
706 Inghardt, T., Potassium channel blocking 1,2-bis(aryl)ethane-1,2-diamines
707 active as antiarrhythmic agents. *Bioorg. Med. Chem. Lett.* **2019**, *29*, (10),
708 1241-1245.
- 709 107. Banerjee, S.; Adhikari, N.; Amin, S. A.; Jha, T., Histone deacetylase 8
710 (HDAC8) and its inhibitors with selectivity to other isoforms: An overview.
711 *Eur. J. Med. Chem.* **2019**, *164*, 214-240.

712 108. Zhao, Z.; Song, H.; Xie, J.; Liu, T.; Zhao, X.; Chen, X.; He, X.; Wu, S.; Zhang,
713 Y.; Zheng, X., Research progress in the biological activities of
714 3,4,5-trimethoxycinnamic acid (TMCA) derivatives. *Eur. J. Med. Chem.* **2019**,
715 173, 213-227.

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