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REVIEW ARTICLE

Opening closed inward rectifier potassium channel doors

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Inwardly rectifying potassium (K_{IR}) channels are essential regulators of membrane potential in excitable and non-excitable tissues. Although K_{IR} channels exhibit a biophysical preference for potassium influx due to voltage-dependent block of outward current by polyamines and Mg^{2+}, under physiological conditions, they predominantly mediate K^+ efflux. This outward current not only is essential for stabilizing the resting membrane potential, limiting cellular excitability and coordinating rhythmic activity in excitable tissues such as the heart and muscle, but also functions in endocrine and exocrine organs and neural tissues. A growing list of pathogenic K_{IR} mutations that reduce or abolish channel activity has been linked to channelopathies, including Andersen syndrome and EAST/SeSAME syndrome, among others. These loss-of-function phenotypes underscore the therapeutic need for selective K_{IR} channel activators. However, pharmacological tools remain limited and subtype-selective activation is rare. Small molecules such as ML297 selectively activate $K_{ir}3.1/3.2$-containing channels, whereas GiGA1 and VU0529331 target $K_{ir}3.2$-containing subunits. Several clinically used drugs (e.g. propafenone) modulate $K_{ir}2.1$ and novel compounds such as GPV0057 show improved selectivity. However, no K_{IR} channel activators have advanced to clinical trials and key subtypes such as $K_{ir}1.1$ and $K_{ir}7.1$ lack known openers. This review evaluates the current knowledge of K_{IR}-targeted agonists, with a focus on their potential to address PIP_2-dependent loss-of-function mutations in K_{IR} channels. We emphasize the urgent need for subtype-specific K_{IR} openers, the development of PIP_2-independent mechanisms of action and comprehensive preclinical characterization to overcome translational barriers. Addressing these challenges may provide new therapeutic opportunities for rare channelopathies associated with K_{IR} channel dysfunction.

KEYWORDS
diseases, openers, PIP_2, pharmacology, potassium channels

1 | INTRODUCTION

1.1 | Inward rectifier K^+ channels

K^+ channels are encoded by about 80 genes, making them the largest family among ion channels. The encoded proteins can assemble in homomeric or heteromeric forms, resulting in over 80 functional

Abbreviations: ADMET, absorption, distribution, metabolism, excretion, toxicity; EAST/SeSAME, epilepsy, ataxia, sensorineural deafness and tubulopathy syndrome/seizures, epilepsy, ataxia, sensorineural deafness and tubulopathy syndrome; GIRK, G protein-coupled inwardly rectifying potassium channel ($K_{ir3.x}$); $G_{\beta\gamma}$, G-protein beta-gamma complex; hERG, human ether-a-go-go-related gene; I_{K1}, inward rectifier potassium current; K_{ATP}, ATP-sensitive potassium channel ($K_{ir}6.x$, which combine with sulfonylurea receptors (SUR1-3); SUMO, small ubiquitin-like modifier; SUMOylation, process of attachment or detachment of SUMO to proteins; SUR, sulfonylurea receptor; TM, transmembrane segment; TMD, transmembrane domain.

proteins. These channels are involved in a wide variety of physiological processes. By controlling K^+ ion homeostasis, they ensure the proper membrane potential for an appropriate and efficient cell response. Within this large class of ion channels, the **inward rectifier K^+ channel (K_{IR})** family comprises seven members (K_{ir}1.x to K_{ir}7.x) encoded by 16 genes (*KCNJ*). Based on sequence homology, these can be divided into four functional classes: classical K_{IR} channels (K_{ir}2.x), G-protein coupled K_{ir} channels (K_{ir}3.x), ATP-sensitive K^+ channels (K_{ir}6.x) and K^+ transport channels (K_{ir}1.x, K_{ir}4.x, K_{ir}5.x, K_{ir}7.x). K_{IR} channels are ubiquitously expressed and underlie a variety of physiological functions such as electrical activity in muscles, neurons and the heart, electrolyte homeostasis and insulin release.

This family is characterized by the ability to conduct K^+ ions more easily into the cell rather than out of it. On the one hand, strong conductance at negative potentials ensures that cells maintain a stable resting membrane potential upon hyperpolarizing factors. However, weak conductance at depolarizing potentials prevents excessive outward K^+ current during the action potential in excitable cells such as cardiac myocytes. This rectification property is mediated via blockage by intracellular polyamines and Mg^{2+} ions (Hibino et al., 2010).

1.2 | Structural features of K_{IR} channels

K_{IR} subunits each have two transmembrane segments, TM1 and TM2, that surround the pore domain, with intracellular N- and C-termini. Four subunits assemble to form a functional channel. Recent successes in X-ray and cryo-EM methods have enabled the elucidation of multiple 3D structures, including human **K_{ir}2.1** in the closed state (Fernandes et al., 2022), chicken **K_{ir}2.2** in closed and open conformations (Hansen et al., 2011; Lee et al., 2016; Zangerl-Plessl, Lee, et al., 2019) and mouse **K_{ir}3.1** (Nishida et al., 2007), **K_{ir}3.2** (Niu et al., 2020) and **K_{ir}6.1** and **K_{ir}6.2** channels in both states (Ding et al., 2019; Martin et al., 2017; Zhao & MacKinnon, 2021). Near-atomic cryo-EM structures of full-length **K_{ir}4.1** in complex with dynein light chains (Lee et al., 2025) and **K_{ir}7.1** are available in a preprint (https://doi.org/10.1101/2024.06.07.597981). Figure 1 not only shows remarkable conservation of the pore module but also highlights the diverse accessory regulators of the family and fine-tuned structural differences. A list of currently published 3D structures is shown in Table S1.

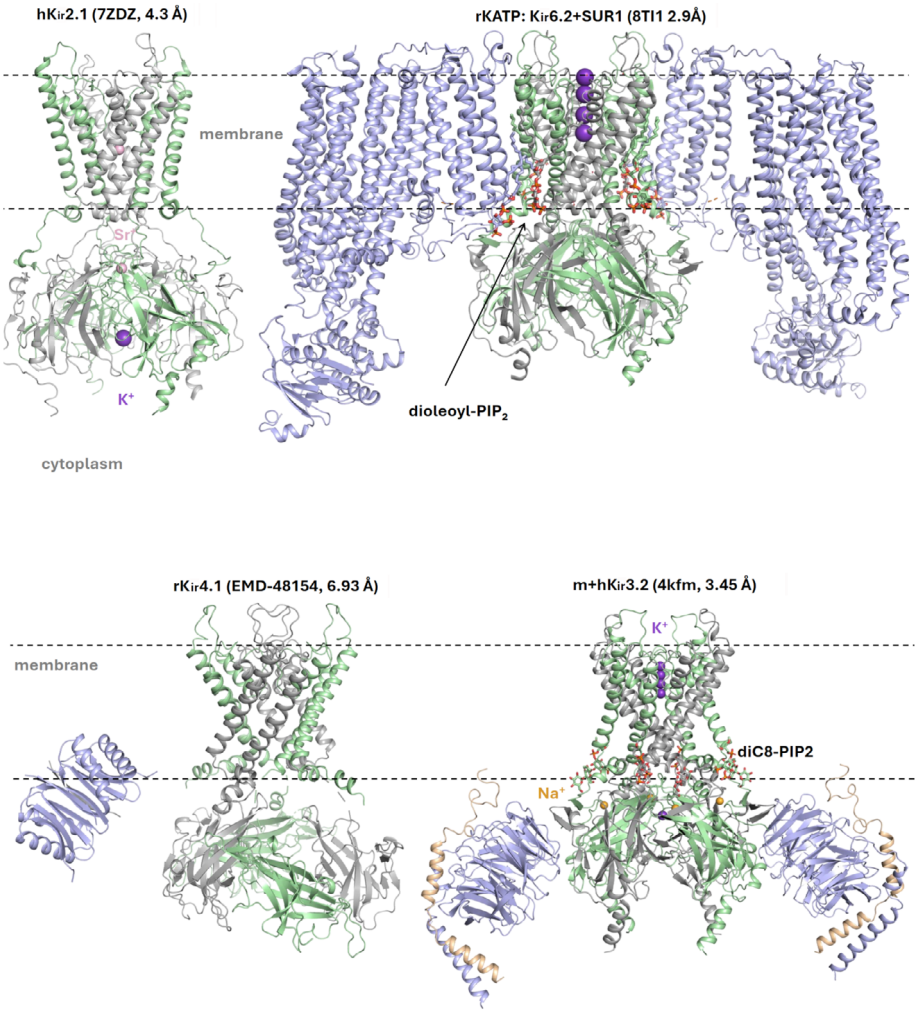


FIGURE 1 Side view of selected experimentally determined K_{IR} structures. Structures generated with PyMOL. K_{IR} structures are shown in green/grey. Purple coloured domains correspond to SUR1 subunits in the K_{ir}6.2 complex, dynein light chain 1 dimer in the K_{ir}4.1 complex and G_β in the K_{ir}3.2 complex; additionally, G_γ is coloured orange. Purple spheres represent K^+ ions, whereas pink ones represent Sr^+ ions and orange ones represent Na^+ ions.

Furthermore, both homotetrameric and heterotetrameric channels can be formed, for example, $K_{ir}2.1/2.2$ (Zobel et al., 2003) or $K_{ir}4.1/$**5.1** (Pessia et al., 1996), further increasing the number of functional channels. K_{IR} channel subfamilies are gated by distinct ligands such as $G_{\beta\gamma}$ and Na^+ ($K_{ir}3$), H^+ ($K_{ir}1/K_{ir}4/K_{ir}5$), nucleotides and sulfonylurea receptor (SUR) subunits ($K_{ir}6$), and with **PIP_2** as a universal activator (Hibino et al., 2010). Potassium permeation is regulated by three gates: – the selectivity filter, helix bundle crossing (HBC) and G-loop. The helix bundle crossing gate, formed by TM2 helices, opens via helix bending and rotation to allow ion flow. The G-loop gate, located at the cytoplasmic domain (CTD), undergoes conformational changes increasing its diameter to permit passage (Whorton & MacKinnon, 2011). Intracellular domains mediate ligand interactions: for example $G_{\beta\gamma}$ binding partially dilates the G-loop, but full opening requires PIP_2 stabilization, as detailed in the next section.

1.3 | The essential role of PIP_2 in K_{IR} channel activation

Phosphatidylinositol-4,5-bisphosphate (PIP_2) is a critical activator of all K_{IR} channels. Structural, functional and computational studies across K_{IR} subtypes, including $K_{ir}2.2$ (Hansen et al., 2011; Lee et al., 2016; Zangerl-Plessl, Lee, et al., 2019), $K_{ir}3.2$ (Wang et al., 2014; Whorton & MacKinnon, 2011, 2013) and $K_{ir}6.2$ in K_{ATP} channels (Driggers et al., 2024; Shyng et al., 2000) have identified a conserved PIP_2 binding site at the interface between transmembrane domain (TMD) and cytoplasmic domain. This site is fully formed only when the cytoplasmic domain adopts a 'compact and engaged' conformation, involving upward and rotational movement, aligning the cytoplasmic domain with the TMD to enable high-affinity PIP_2 binding. PIP_2 binding, in turn, stabilizes open or pre-open states by promoting structural changes in the helix bundle crossing and G-loop gates, for example (Bründl et al., 2021; Driggers et al., 2024; Hansen et al., 2011; Nguyen et al., 2026; Niu et al., 2020; Pipatpolkai et al., 2022). Despite this conserved mechanism, K_{IR} subtypes differ in how PIP_2 regulates gating. In $K_{ir}2$ channels, PIP_2 binding induces pronounced cytoplasmic domain rearrangements that stabilize the open state (Hansen et al., 2011; Lee et al., 2016). However, the presence of secondary anionic lipids is essential to fully potentiate PIP_2-dependent channel activation in this subfamily (Lee et al., 2016). In contrast, $K_{ir}3$ (GIRK) channels undergo more modest cytoplasmic domain movements in response to PIP_2, which must be complemented by binding of G-protein βγ subunits, revealing another dual regulation mechanism unique to this subtype (W. Wang et al., 2014; Whorton & MacKinnon, 2011, 2013). The situation is even more complex in $K_{ir}6$ channels, which, together with SURs form octameric K_{ATP} channels. Here, gating is controlled by both PIP_2 and **ATP**, with PIP_2 acting to relieve ATP-mediated inhibition. Notably, ATP and pharmacological inhibitors stabilize a compact but disengaged conformation, where the cytoplasmic domain remains close to the membrane yet misaligned with the PIP_2 binding site, functionally preventing activation (Driggers et al., 2024). Recent cryo-EM data further reveal a non-canonical PIP_2 binding site at the $K_{ir}6.2$-**SUR1** interface, suggesting that channel gating involves cooperative interactions between the K_{IR} pore and its regulatory SUR subunit (Driggers et al., 2024). Structural comparisons between closed and open K_{ATP} channels show minimal changes at the G-loop gate, suggesting that in $K_{ir}6$ channels this gate may not constitute a barrier to ion conduction (Martin et al., 2017).

Surprisingly, a $K_{ir}2.1$ cryo-EM structure, solved in the absence of PIP_2, exhibits cytoplasmic domain rearrangements similar to PIP_2-bound states (Fernandes et al., 2022). This raises the possibility that PIP_2 may stabilize rather than trigger these conformational changes and that the intrinsic dynamics of the channel protein, along with other lipids or auxiliary partners such as anionic lipids in $K_{ir}2$, SUR1 in $K_{ir}6$ or $G_{\beta\gamma}$ in $K_{ir}3$, play a major role in channel gating.

In **$K_{ir}1.1$** and $K_{ir}4.1/K_{ir}5.1$ channels, PIP_2-dependent gating is further modulated by intracellular pH. Acidification decreases apparent PIP_2 affinity and favours closed states, whereas alkaline pH stabilizes PIP_2-bound open conformations (Pessia et al., 2001; Rapedius et al., 2007). This dual dependence on PIP_2 and pH provides an additional regulatory axis unique to these K_{IR} subfamilies and may represent another opportunity for pharmacological intervention. A comparative overview of PIP_2-dependent gating mechanisms, cofactors, disease associations and implications for activator action across K_{IR} subfamilies is summarized in Table 1.

Unfortunately, to date, no high-resolution structures of wild-type K_{IR} channel in fully open states without gating-facilitating mutations have been obtained. This limits our understanding of how PIP_2 binding transitions into pore opening under physiological conditions. A clearer understanding of these structural changes and the steps they involve will be important for designing targeted small-molecule activators that mimic or stabilize key gating states. This will be particularly important for loss-of-function (LOF) mutations, leading to disrupted PIP_2-dependent gating (for a list of disease mutations with impaired PIP_2 binding, see Tables 2, 3, 4, 5, 6 and 7). As shown in Tables 2–7, disease mutations that disrupt PIP_2 binding have been reported across five different K_{IR} subfamilies. The majority of these mutations occur in $K_{ir}2.1$, associated with Andersen's syndrome, where approximately 60% of disease-causing mutations operate via this mechanism. In the following section, the pathophysiology of K_{IR} channels is summarized briefly.

2 | PATHOPHYSIOLOGY

Comprehensive reviews detailing the structure, cell biology, physiology and pharmacology of inward rectifier potassium (K_{IR}) channels are available (Cheng et al., 2015; Cui et al., 2021; Gutiérrez et al., 2024; Hibino et al., 2010; Nichols, 2025; Zangerl-Plessl, Qile, et al., 2019; Zhao & MacKinnon, 2021). Accordingly, we provide only a brief overview here, focusing instead on the pathophysiological consequences of loss-of-function mutations in K_{IR} channels, particularly where these mutations impair PIP_2-dependent activation gating, which may be

TABLE 1 Comparative overview of PIP_2-dependent gating across K_{IR} subfamilies.

K_{IR} subfamily	Relative PIP_2 affinity	Additional co-factors	Characteristic gating features	Disease mutations impairing PIP_2 coupling	Relevance for activator action
$K_{ir}1.1$ (ROMK)	Medium	Intracellular pH	PIP_2 stabilizes open state; acidification reduces PIP_2 affinity	Yes (Bartter syndrome)	Strongly PIP_2-dependent; no activators known
$K_{ir}2.x$	High	Anionic lipids enhance PIP_2 action	CTD compaction essential; robust PIP_2 sensitivity	Yes (Andersen syndrome)	PIP_2-dependent; modulators likely enhance PIP_2 coupling.
$K_{ir}3.x$ (GIRK)	Lower	$G\beta\gamma + PIP_2$ co-requirement	Dual ligand gating; modest CTD movement	Yes (various arrhythmias)	All known activators require intact PIP_2 binding.
$K_{ir}4.1$, $K_{ir}4.1/K_{ir}5.1$	Medium–low	pH (strong modulation)	PIP_2-dependent; pH shifts PIP_2 affinity	Yes (EAST/SeSAME)	Activators depend on functional PIP_2 gating.
$K_{ir}6.x$ (KATP)	Low–medium	ATP, SUR, Mg-nucleotides	PIP_2 counteracts ATP inhibition; SUR allosterically regulates gating	Yes (CHIs, neonatal diabetes)	Most activators act via SUR; CL-705G may partly bypass PIP_2.
$K_{ir}7.1$	Low	None known	Weak rectification, slow gating; low PIP_2 affinity	Yes (snowflake VRD)	No activators known; pharmacologically underexplored

Abbreviation: CHIs, congenital hyperinsulinism; CTD, cytoplasmic domain; VRD, vitreoretinal degeneration.

TABLE 2 $K_{ir}1.1$ (*KCNJ1*) disease mutations with impaired PIP_2 regulation linked to Bartter syndrome type II (OMIM: 241200).

Subtype	Mutation	Functional data	Species	Reference
$K_{ir}1.1$	I51T	Loss of function, decreased PIP_2 binding	Human	(Lopes et al., 2002)[a] (Schulte et al., 1999)[b]
$K_{ir}1.1$	A214V	Loss of function, decreased PIP_2 binding	Human	(Lopes et al., 2002)[a] (Martelli-Júnior et al., 2012)[b]
$K_{ir}1.1$	S219A (S > R)	Loss of function, decreased PIP_2 affinity (increase sensitivity to anti-PIP_2 antibody & heptalysine)	Human	(Leung et al., 2000; Liou et al., 1999)[a] (Srivastava et al., 2013)[b] (Simon et al., 1996)[c]
$K_{ir}1.1$	S219D (S > R)	Loss of function, mimics phosphorylation charge but does not enhance PIP_2 binding, highly sensitive to PIP_2 depletion	Human	(Lopes et al., 2002)[a] (Srivastava et al., 2013)[b] (Simon et al., 1996)[c]
$K_{ir}1.1$	L220F	Loss of function (WT + L220F heteromers resemble WT), decreased PIP_2 binding	Human	(Lopes et al., 2002; Srivastava et al., 2013)[a] (Schulte et al., 1999)[b]

[a]Functional data reference.
[b]Disease association reference.
[c]Additional disease association reference.

pharmacologically targetable. Loss-of-function mutations in K_{IR} channels have been documented to be associated with many disorders:- **Bartter's syndrome type 2**, antenatal (OMIM: 241200, *KCNJ1*, $K_{ir}1.1$), presents with severe renal salt-wasting causing premature birth, foetal polyuria, polyhydramnios and postnatal hypokalaemic metabolic alkalosis with transient hyperkalaemia, hypercalciuria and nephrocalcinosis. Secondary features include dehydration, muscle weakness and osteopenia (Bartter et al., 1962; Qasba et al., 2023; Seyberth et al., 2017); **Andersen's syndrome** (OMIM: 170390, *KCNJ2*, $K_{ir}2.1$) is characterized by periodic paralysis, ventricular arrhythmias (long QT), facial and skeletal dysmorphisms and neurocognitive abnormalities (Bendahhou et al., 2003; Goslinga et al., 2024; Nguyen et al., 2013; Tawil et al., 1994); Keppen–Lubinsky syndrome (OMIM: 614098, *KCNJ6*, $K_{ir}3.2$) manifests with developmental delay, postnatal growth failure, generalized lipodystrophy, hypertonia, distinctive aged facial appearance with tightly adherent thin skin, pinched nose, hypoplastic alae nasi, short philtrum and tented upper lip (Hamilton & Suri, 2020; Masotti et al., 2015); **long QT syndrome 13** (OMIM: 613485, *KCNJ5*, **$K_{ir}3.4$**) patients exhibit prolonged QT interval and may develop recurrent syncope, atrial fibrillation or tachycardia (Bohnen et al., 2017; Wang et al., 2013; Yang et al., 2010); EAST/SeSAME syndrome (OMIM: 612780, *KCNJ10*, $K_{ir}4.1$), the main clinical features include epilepsy, ataxia, sensorineural deafness and renal salt wasting tubulopathy (Abdelhadi et al., 2016; Bockenhauer et al., 2009; Lo et al., 2022; Scholl et al., 2009); hypokalaemic tubulopathy and deafness (OMIM: 619406, *KCNJ16*, $K_{ir}5.1$) is characterized by renal salt wasting tubulopathy, severe hypokalaemia, metabolic acidosis or alkalosis, sensorineural hearing loss, fatigue, salt craving, polyuria, while

TABLE 3 $K_{ir}2.1$ (*KCNJ2*) disease mutations with impaired PIP_2 regulation linked to Andersen syndrome/long QT syndrome 7 (LQT7, OMIM: 170390).

Subtype	Mutation	Functional data	Species	Reference
$K_{ir}2.1$	C54F	Loss of function, likely interferes with PIP_2 binding, dominant-negative effect, normal trafficking	Human	(Bendahhou et al., 2007)[a,b]
$K_{ir}2.1$	R67W (R > Q)	Loss of function, increased sensitivity to PIP_2 depletion dominant-negative effect, R67Q: PIP_2 binding similar to WT	Human	(D'Avanzo et al., 2013; Handklo-Jamal et al., 2020)[a] (Andelfinger et al., 2002)[b] (Haruna et al., 2007)[c]
$K_{ir}2.1$	D71V (D > A, N, Y)	Loss of function, no decrease in strength of PIP_2 interactions, dominant-negative effect, no trafficking defects	Human	(Bendahhou et al., 2003; Lopes et al., 2002)[a] (Canún et al., 1999)[b] (Donaldson et al., 2003; Marrus et al., 2011; Villar-Quiles et al., 2022)[c]
$K_{ir}2.1$	V77E	Loss of function, impaired PIP_2 regulation, no trafficking defects, dominant-negative effect	Human	(Handklo-Jamal et al., 2020)[a,b]
Kir2.1	C122Y	Loss of function, decreased PIP_2 binding, destabilizes PIP_2 binding site (disrupts C122-C154 disulfide bond), dominant-negative effect	Human	(Cruz et al., 2024)[a,b]
$K_{ir}2.1$	C154F	Loss of function, disrupts C122-C154 disulfide bond (destabilizes PIP_2 binding site?), dominant-negative effect	Human	(Cruz et al., 2024; Villar-Quiles et al., 2022)[a] (Bendahhou et al., 2005)[b]
$K_{ir}2.1$	C154Y	Loss of function, disrupts C122–C154 disulfide bond, does not impact PIP_2 binding (similar to WT), diminished surface expression, dominant-negative effect	Human	(Zuniga et al., 2024)[a] (Sacconi et al., 2009)[b]
$K_{ir}2.1$	P186A	Loss of function, reduced PIP_2 binding	Mouse	(Soom et al., 2001)[a]
$K_{ir}2.1$	P186Q (P > L, T)	Loss of function, PIP_2 binding motif (P186 mouse is analogue to human), dominant-negative effect	Human	(Le Tanno et al., 2021)[a,b] (Song et al., 2016; Tristani-Firouzi et al., 2002)[c]
$K_{ir}2.1$	K187Q (K > R)	Loss of function, PIP_2 binding similar to WT, increased PIP_2 did not rescue the mutation, K187 contributes positive charge to PIP_2 binding	Human	(D'Avanzo et al., 2013; Lopes et al., 2002)[a] (Delannoy et al., 2013)[c]
$K_{ir}2.1$	R189I (R > S)	Loss of function, decreased PIP_2 binding (inferred, K189Q decreased PIP_2 binding) K189Q: Decreased PIP_2 binding	Human	(D'Avanzo et al., 2013; Donaldson et al., 2004; Lopes et al., 2002)[a] (Donaldson et al., 2003)[b] (Song et al., 2016)[c]
$K_{ir}2.1$	N216H	Loss of function, dominant-negative effect, no trafficking defects, N216D decreased PIP_2 sensitivity (mouse)	Human	(Bendahhou et al., 2003; Epshtein et al., 2009)[a] (Tristani-Firouzi et al., 2002)[b]
$K_{ir}2.1$	R218W (R > P, L)	Loss of function, decreased PIP_2 binding	Human	(Cruz et al., 2024)[a] (Plaster et al., 2001)[b] (Stunnenberg et al., 2018; Van Ert et al., 2016)[c]
$K_{ir}2.1$	R218Q (R > P, L)	Loss of function, decreased PIP_2 binding, dominant-negative effect, co-assembles with WT, membrane localized	Human	(Bendahhou et al., 2003; D'Avanzo et al., 2013; Lopes et al., 2002)[a] (Plaster et al., 2001)[b] (Stunnenberg et al., 2018; Van Ert et al., 2016)[c]
$K_{ir}2.1$	G300V (G > A)	Loss of function, decreased PIP_2 binding, dominant-negative effect, co-assembles with WT, membrane localized	Human	(Bendahhou et al., 2003; Lopes et al., 2002)[a] (Plaster et al., 2001)[b] (Díaz-Manera et al., 2011)[c]
$K_{ir}2.1$	G300D (G > A)	Loss of function; mutation in the G-loop affecting lower gate flexibility; altered hydrogen bonding with T309; perturbs PIP_2 regulation indirectly via gating	Human	(Bendahhou et al., 2003; Munawar et al., 2025)[a] (Donaldson et al., 2004)[b] (Díaz-Manera et al., 2011)[c]
$K_{ir}2.1$	V302M (V > del)	Loss of function, decreased PIP_2 binding (allosteric?) dominant-negative effect, no trafficking or assembly defects	Human	(Bendahhou et al., 2003; Tristani-Firouzi et al., 2002)[a,b] (Ördög et al., 2015)[c]
$K_{ir}2.1$	E303K	Loss of function, decreased PIP_2 binding (allosteric), dominant-negative effect	Human	(Bendahhou et al., 2003; Lopes et al., 2002)[a] (Plaster et al., 2001)[b]
$K_{ir}2.1$	M307I	Loss-of-function, reduced PIP_2 binding, dominant negative effect; M307L functional, PIP_2 sensitivity similar to WT	Human	(Handklo-Jamal et al., 2020; Tan et al., 2013)[a] (Choi et al., 2007)[b]
$K_{ir}2.1$	M307V	Loss-of-function, high sensitivity to PIP_2 depletion, dominant negative effect	Human	(Handklo-Jamal et al., 2020)[a] (Liu et al., 2015)[b]

(Continues)

TABLE 3 (Continued)

Subtype	Mutation	Functional data	Species	Reference
$K_{ir}2.1$	T309I	Loss of function, dominant-negative effect, no trafficking defects, altered hydrogen bonding with G300, perturbs PIP_2 regulation indirectly via gating, increased PIP_2 concentration did not rescue the mutation	Human	(Bendahhou et al., 2005)[a,b]

[a]Functional data reference.
[b]Disease association reference.
[c]Additional disease association reference.

TABLE 4 $K_{ir}4.1$ (*KCNJ10*) disease mutations with impaired PIP_2 regulation linked to EAST/SeSAME (OMIM: 612780).

Subtype	Mutation	Functional data	Species	Reference
$K_{ir}4.1$	R175Q	Loss of function, reduced PIP_2 affinity, flickering, with strongly decreased mean open time, alkaline shifted pH sensitivity	Human	(Reichold et al., 2010)[a,b] (Nicita et al., 2018)[a]
$K_{ir}4.1$	R297C	Loss of function, inferred decreased PIP_2 binding, alkaline shifted pH sensitivity, analogous to R292W $K_{ir}1.1$ BS1 (LOF) & R312Q $K_{ir}2.1$ AS1 (LOF, weak PIP_2 interaction)	Human	(Sala-Rabanal et al., 2010; Williams et al., 2010)[a] (Scholl et al., 2009)[a,b]

Abbreviations: AS1, Andersen's syndrome type 1; LOF, loss-of-function.
[a]Functional data reference.
[b]Disease association reference.

TABLE 5 $K_{ir}6.2$ (*KCNJ11*) disease mutations with impaired PIP_2 regulation linked to hyperinsulinemic hypoglycaemia familial 2 (HHF2, OMIM: 601820).

Subtype	Mutation	Functional data	Species	Reference
$K_{ir}6.2$	R176C (R > H)	Loss of function, decreased PIP_2 sensitivity, functionally uncoupled from SUR1	Human	(John et al., 2001)[a] (Flechtner et al., 2006)[b] (Szymanowski et al., 2016)[c]
$K_{ir}6.2$	R177W	R177A: Loss of function, decreased PIP_2 affinity	Human	(Shyng et al., 2000)[a] (Arya et al., 2014)[b]
$K_{ir}6.2$	R195A (R > H)	Loss of function, decreased PIP_2 sensitivity	Human	(Shyng et al., 2000)[a] (Salomon-Estebanez et al., 2016)[c]
$K_{ir}6.2$	R206A (R > C, H, L)	Loss of function, decreased PIP_2 regulation, rescued only at high PIP_2 concentration (100 μg/ml), reduced open state stability	Human	(Shyng et al., 2000)[a] (Bennett et al., 2015; Boodhansingh et al., 2019; Salomon-Estebanez et al., 2016)[c]
$K_{ir}6.2$	R301A (R > G, H, P)	Loss of function, reduced PIP_2 response	Human	(Shyng et al., 2000)[a] (Lin et al., 2008)[b,c] (Stanley et al., 2004)[c]
$K_{ir}6.2$	R301C (R > G, H, P)	Loss of function, reduced PIP_2 sensitivity	Human	(John et al., 2001)[a] (Lin et al., 2008)[b,c]

[a]Functional data reference.
[b]Disease association reference.

lacking neurological symptoms (Schlingmann et al., 2021); **hyperinsulinemic hypoglycaemia, familial 2** (OMIM: 601820, *KCNJ11*, $K_{ir}6.2$) presents with neonatal/infant onset, protein or fasting induced hypoglycaemia and is **diazoxide** responsive (Senniappan et al., 2013; Yavas Abali et al., 2025); **maturity-onset diabetes of the young, type 13** (OMIM: 616329, *KCNJ11*, $K_{ir}6.2$) is characterized by early-onset diabetes, impaired insulin secretion, negative autoimmune markers, normal BMI and respond well to sulfonylurea (Antal, 2021); **diabetes mellitus, permanent neonatal 2** (with or without neurologic features) (OMIM: 618856, *KCNJ11*, $K_{ir}6.2$) manifests with impaired insulin

TABLE 6 $K_{ir}7.1$ (*KCNJ13*) disease mutations with impaired PIP_2 regulation linked to snowflake vitreoretinal degeneration (OMIM: 193230).

Subtype	Mutation	Functional data	Species	Reference
7.1	R162W	Loss of function; dominant-negative effect, disrupts PIP_2 binding and TMD-CTD coupling R > A, C → gain of function R > F → abolished function R > Q → loss of function Suggests volume dependency	Human	(Hernandez et al., 2023; Vera et al., 2021; W. Zhang et al., 2013)[a] (Hejtmancik et al., 2008)[b]

[a]Functional data reference.
[b]Disease association reference.

TABLE 7 $K_{ir}7.1$ (*KCNJ13*) disease mutations with impaired PIP_2 regulation linked to Leber congenital amaurosis (OMIM: 614186).

Subtype	Mutation	Functional data	Species	Reference
7.1	R162Q	Loss of function; dominant-negative effect, disrupts PIP_2 binding and TMD-CTD coupling R > A, C → gain of function R > F → abolished function R > Q → loss of function Suggests volume dependency	Human	(Hernandez et al., 2023; Vera et al., 2021; Zhang et al., 2013)[a] (Sergouniotis et al., 2011)[b]
7.1	R166C (R > term)	Loss of function, destabilizes PIP_2 binding site, no trafficking defects	Human	(Vera et al., 2021)[a] (Sergouniotis et al., 2011)[b]

[a]Functional data reference.
[b]Disease association reference.

secretion, hyperglycaemia, negative autoimmune markers. Some patients showed ketoacidosis, severe developmental delay, muscle weakness, epilepsy and mild dysmorphic features (Gloyn et al., 2004); **diabetes mellitus, transient neonatal 3** (OMIM: 610582, *KCNJ11*, $_{Kir}6.2$); **Leber congenital amaurosis 16** (OMIM: 614186, *KCNJ13*, $K_{ir}7.1$) is characterized by severe early-onset visual impairments, nystagmus, photophobia, retinal pigmentation abnormalities (macula involvement), attenuated retinal vasculature and severely reduced electroretinogram (Pattnaik et al., 2015); and **snowflake vitreoretinal degeneration** (OMIM: 193230, *KCNJ13*, $K_{ir}7.1$) presents with snowflake-like retinal deposits, focal retinal pigment epithelium degeneration, moderate myopia and vitreal volume increase (Pattnaik et al., 2013) (Tables 2–7).

As shown in Tables 2–7, disruption of PIP_2-channel interactions has been shown to underlie the loss-of-function phenotype in a considerable number of missense variants. This mechanism has been specifically implicated in selected mutations associated with Andersen's syndrome, Bartter's syndrome (Lopes et al., 2002), EAST syndrome (Reichold et al., 2010), congenital hyperinsulinism (Giri et al., 2022; Senniappan et al., 2013) and snowflake vitreoretinal degeneration (Pattnaik et al., 2013).

A recent study identified that hypoxia-induced SUMOylation and the Andersen·s syndrome type 1 (AS1)-linked variant R67Q independently and co-operatively suppress $K_{ir}2.1$ function by weakening PIP_2 interactions, thereby reducing current amplitude (Chandrashekar et al., 2025). Inhibition of the SUMO (small ubiquitin-like modifier) pathway (e.g. with **TAK-981**) restored channel activity, suggesting that stress-induced modifications and pathogenic variants may act synergistically through a shared PIP_2-dependent gating defect.

Other mechanisms contributing to loss-of-function include defective channel forward trafficking, as reviewed in Zangerl-Plessl, Qile, et al. (2019). In such cases, chaperone-based therapies may be required to restore proper surface expression and function, whereas inhibiting $K_{ir}2.1$ channel degradation also results in increased $K_{ir}2.1$ currents (Ji, Takanari, et al., 2017).

In most of these disorders, there are currently no effective treatments available that directly restore normal K_{IR} channel function. K_{IR} activators may provide promising therapeutic options for K_{IR} loss-of-function mutations, including those that result from impaired PIP_2 regulation. However, their clinical potential depends on several critical factors such as the type and severity of the mutation, the specificity of the compound and its safety profile. These challenges are not unique to K_{IR} channels and reflect broader issues common across the pharmacology of potassium channels.

To better understand the therapeutic potential and challenges of K_{IR}-targeted drug development, we first provide a brief impression of potassium channel pharmacology and then narrow our focus to the K_{IR} channel family specifically.

3 | PHARMACOLOGY OF K^+ CHANNELS

K^+ channels share structural motifs that complicate their pharmacology. Many pharmacological molecules show limited specificity between K^+ channel subtypes, making the development of selective drugs for individual channels highly challenging. Although blockers targeting K^+ channels are relatively common, activators are rare and often exhibit low potency, poor selectivity and suboptimal drug-like

properties, including unfavourable absorption, distribution, metabolism, excretion, toxicity (ADMET) profiles. These limitations have hindered the clinical development of K^+ channel activators.

The inward rectifier K^+ (K_{IR}) channel family exemplifies these challenges. While advances in genome sequencing, patch-clamp techniques and high-throughput screening have enabled the identification of novel compounds targeting K_{IR} channels, most of these compounds are blockers. The discovery of effective and selective activators for K_{IR} channels remains limited (see Table 8 for a list of known K_{IR} openers), further underscoring the need for innovative pharmacological approaches.

As most K_{IR}-linked pathologies reflect reduced channel function, strategies aimed at pharmacological modulation have become an attractive therapeutic concept.

3.1 | Inward rectifier K^+ channel blockers

This review is more focused on K_{IR} channel openers but will briefly discuss in this section some of the K_{IR} channel blockers (Table S2).

3.1.1 | Early and non-specific blockers

Early and classical K_{IR} channel blockers share two properties: weakness and non-specificity. Indeed, K_{IR} channels show low sensitivity to **tetraethylammonium (TEA)** but at a millimolar level and are insensitive to **4-aminopyridine (4-AP; fampridine)**, which is a broad-spectrum blocker of the **K_v channels** (reviewed in Walsh, 2020).

3.1.2 | Divalent cation blockers

However, K_{IR} channels are more specifically blocked by certain cations such as barium (Ba^{2+}), a universal K_{IR} channel blocker at the micromolar range (Hagiwara et al., 1978; Rusconi Trigueros et al., 2018). **Barium** is, however, not very selective within the seven K_{IR} channel families.

3.1.3 | Clinically used multichannel blockers

Quinidine and **flecainide** (the latter depending on its dose, see below) are two blockers of the K_{IR} channel family and are used clinically to terminate atrial fibrillation as a Class IA antiarrhythmic drug. However, it is well documented they are multichannel inhibitors (Tamargo et al., 2004).

Sulfonylureas, like **glibenclamide**, interact with ATP-inhibited K^+ channels ($K_{ir}6$) in the pancreas, which induce insulin release, and produce therapeutic effects in diabetes.

Propafenone, an antiarrhythmic drug, was shown to inhibit $K_{ir}2$ channels at certain doses. It has greater efficacy for **$K_{ir}2.3$** compared with $K_{ir}2.2$ and $K_{ir}2.1$, most likely related to differences in PIP_2 affinity (Amorós et al., 2013).

3.1.4 | Repurposed and experimental blockers

The antileishmaniasic drug pentamidine has also $K_{ir}2.1$ inhibiting activity and medium throughput screening efforts yielded a more specific analogue able to inhibit atrial fibrillation in a preclinical animal model (Ji, Varkevisser, et al., 2017; Takanari et al., 2013).

3.1.5 | High-throughput screening

The development of high-throughput screening of large libraries, using fluorescence-based flux and high-throughput patch clamp platforms for K^+ channel modulators, has led to the discovery of new chemicals with certain specificity among the different K_{IR} family members. VU591 was described as the first selective inhibitor of $K_{ir}1.1$, which blocks $K_{ir}1.1$ with an IC_{50} of 8 μmol L^{-1}, without blocking the other K_{IR} family members (Weaver & Denton, 2021). Another specific K_{IR} blocker identified is the ML133 that was at least 10-fold more potent at inhibiting $K_{ir}2.1$ (1.8 μmol L^{-1}) compared with $K_{ir}1.1$ (>300 μmol L^{-1}), $K_{ir}4.1$ (76 μmol L^{-1}) and $K_{ir}7.1$ (33 μmol L^{-1}). However, ML133 does inhibit other members of the $K_{ir}2$ family, $K_{ir}2.2$, $K_{ir}2.3$ and $K_{ir}2.6$, with potencies similar to the inhibition of $K_{ir}2.1$, in the low micromolar range (Wang et al., 2011). Recently, an ML133 derivative (VU6080824) was found to display improved potency (Duncan et al., 2025). As mentioned above, the development of activators for K_{IR} channels has lagged behind. The structural and functional diversity of K_{IR} channels, combined with their sensitivity to intracellular modulators like PIP_2, presents unique challenges for drug discovery. In the following section, we focus on the emerging field of K_{IR} channel activators and their potential to address loss-of-function mutations in K_{IR} channels.

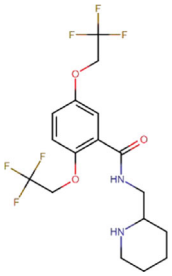
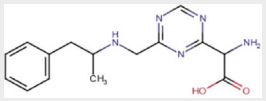
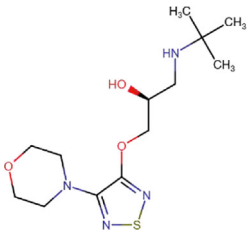
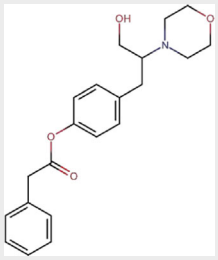
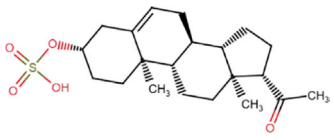
3.2 | Inward rectifier K^+ channels openers

In contrast to the relatively well-studied inhibitors of K_{IR} channels, the discovery and development of specific pharmacological activators (van der Schoor et al., 2020) have received much less attention. K_{IR} openers represent a promising therapeutic strategy for addressing loss-of-function mutations in K_{IR} channels, including those caused by impaired PIP_2 regulation. Research into K_{IR} channel activators has followed three main streams, as detailed below.

Off-target effects of approved drugs: Some drugs, such as **flecainide**, **propafenone** and **timolol**, have been found to activate K_{IR} channels at certain concentrations as an off-target effect. For example, flecainide interacts with Cys311 of $K_{ir}2.1$ homotetramers, reducing channel affinity for polyamines and increasing the outward component of inward rectifier current. However, clinical results have been mixed, with limited efficacy and potential proarrhythmic effects in certain patient populations, such as those with AS1.

Designing novel activators: Medicinal chemistry approaches have led to the development of more selective activators, such as the propafenone analogue GPV0057. GPV0057 has shown improved

TABLE 8 Selection of known K_{IR} channel openers. The degree of selectivity is indicated as ↑ to ↑↑↑ (weak to strong agonistic selectivity), ↓ indicates antagonistic selectivity and × denotes no effect. A structural representation of Avermectin B_{1a} is shown. Note that Ivermectin is a mixture of Avermectin B_{1a} and B_{1b} in an approximately 80/20 ratio.

Drug name	Target	EC_{50}	Selectivity	Comments	Ref.
Flecainide 	↑↑ $K_{ir}2.1$	0.4 ± 0.01 μM	× $K_{ir}2.2$ × $K_{ir}2.3$ × $K_{ir}2.1/2.2$ × $K_{ir}2.1/2.3$	Approved drug, severe side-effects, might be pro-arrhythmic in AS1 patients (mutation dependent)	(Caballero et al., 2010)
Propafenone 	↑↑ $K_{ir}2.1$ (1 μM) (↓ 25 μM)	12.0 ± 3.0 nM	× $K_{ir}2.2$ × $K_{ir}2.3$ × $K_{ir}2.1/2.2$ × $K_{ir}2.1/2.3$ × $K_{ir}2.2/2.3$ ↓ $K_v11.1$ (hERG) ↓ $Na_v1.5$	Approved drug, severe side-effects, might be pro-arrhythmic in AS1 patients (mutation dependent)	(Gómez et al., 2014) (Li et al., 2025)
Timolol 	↑↑↑ Kir2.1	3.2 ± 0.3 nM	N/A	Approved drug, severe side-effects, might be pro-arrhythmic in AS1 patients (mutation dependent)?	(Gómez et al., 2014)
GPV0057 	↑↑↑ $K_{ir}2.1$	N/A	× $K_v11.1$ (hERG) × $Na_v1.5$	Analogue of propafenone with improved selectivity, no ADMET assessment (yet)	(Li et al., 2025)
Pregnenolone sulfate 	↑ $K_{ir}2.3$	15.6 ± 0.9 μM	↑ $K_{ir}2.1/2.3$ ↑ $K_{ir}2.2/2.3$ × $K_{ir}1.1$ × $K_{ir}2.1$ × $K_{ir}2.2$ × $K_{ir}3.1/3.2$ × $K_{ir}2.1/2.2$	Acting only, when applied from EC side	(Kobayashi et al., 2009)

(Continues)

TABLE 8 (Continued)

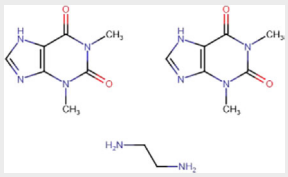
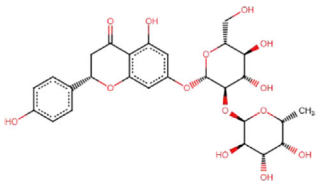
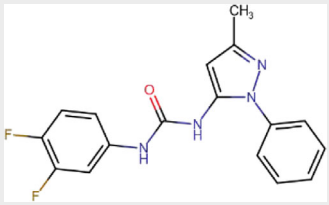
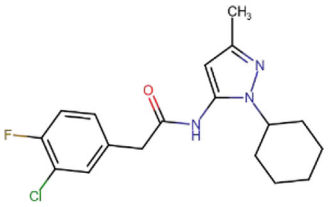
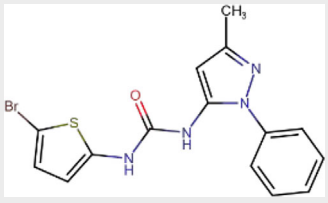
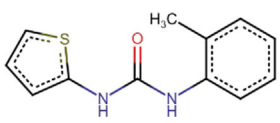
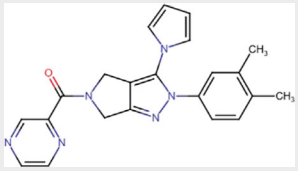
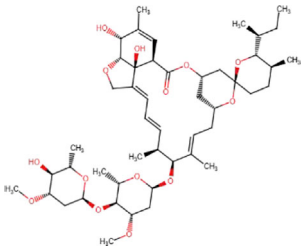
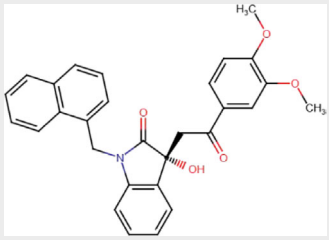
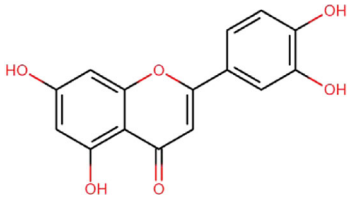
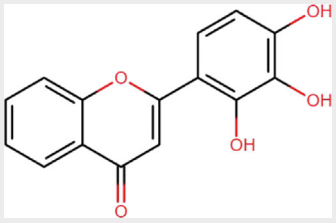
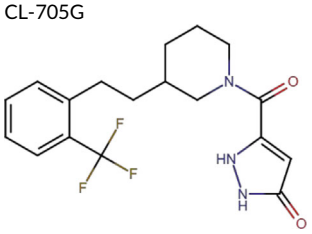
Drug name	Target	EC_{50}	Selectivity	Comments	Ref.
Aminophylline 	$K_{ir}2.x$	N/A	N/A	Complex inhibitory and activatory effects, presumably depending on the heteromeric $K_{ir}2.x$ channel composition	(Ramalho et al., 2022)
Naringin 	↑ $K_{ir}3.1$	$K_{ir}3.1/3.2$ 111.0 μM $K_{ir}3.1/3.$ 120.9 μM	↑ $K_{ir}3.1/3.2$ ↑ $K_{ir}3.1/3.4$	Natural compound in grapefruit, known to interact with other ion channels	(Yow et al., 2011)
ML297 (VU0456810) 	↑↑↑ $K_{ir}3.1/3.2$	HEK whole-cell: 160 nM (Kaufmann et al., 2013) HEK whole-cell: 233 ± 38 nM (Wydeven et al., 2014) HEK whole-cell: 110 nM (Xu et al., 2020)	↑↑ $K_{ir}3.1/3.3$ ↑↑ $K_{ir}3.1/3.4$ ↓ $K_v11.1$ (hERG, at 50 μM) × $GABA_A$ × $K_{ir}3.2$	Likely moderate BBB penetration. **Moderate lipophilicity** and **low molecular weight** may favour brain penetration.	(Kaufmann et al., 2013; Wydeven et al., 2014; Xu et al., 2020)
VU0810464 	↑↑↑ $K_{ir}3.1/K_{ir}3.2$	0.165 ± 0.012 μM	↑ $K_{ir}3.1/3.4$	Likely moderate BBB penetration. **Lipophilic** with **possible issues with high molecular weight**, which could limit BBB crossing.	(Vo et al., 2019; Wieting et al., 2017)
GAT1508 	↑↑↑ $K_{ir}3.1/3.2$	HEK whole-cell: 75 nM ± 10 nM Xenopus oocyte (TEVC): 0.37 ± 0.11 μM	× $K_{ir}3.1/3.4$ × $K_v11.1$ (at 50 μM)	Good BBB penetration expected due to **low molecular weight** and **moderate lipophilicity**. Lower PIP_2 concentration dependency than ML297.	(Xu et al., 2020)
GiGA1 	↑↑↑ $K_{ir}3.1/3.2$	31 μM	↑ $K_{ir}3.1/3.3$ ↑ $K_{ir}3.1/3.4$ × $K_{ir}3.2$ × $K_{ir}3.2/3.3$	Likely **poor BBB penetration** due to **high molecular weight** and **polar groups**.	(Zhao et al., 2020)

TABLE 8 (Continued)

Drug name	Target	EC_{50}	Selectivity	Comments	Ref.
VU0529331 	↑↑↑ $K_{ir}3.2$	5.1 μM	↑↑ $K_{ir}3.1/3.2$ ↑↑ $K_{ir}3.1/3.4$ ↑ $K_{ir}6.1$/SUR2b ↑↑ $K_{ir}6.1$/SUR2a ↑↑ $K_{ir}3.4$ × $K_{ir}4.1$ × $K_{ir}2.1$ × $K_{ir}6.2$/SUR1 × $K_v2.1$ × α1 GlyR × $K_{Ca}4.1$	**Moderate BBB penetration**, though **polar functional groups** could reduce brain penetration.	(Kozek et al., 2019)
Ivermectin 	↑↑↑ $K_{ir}3.1/3.2$	3.5 ± 2.0 μM	↑ $K_{ir}3.1/3.4$ × $K_{ir}3.1/3.3$	Approved drug, good tolerability, but GIRK concentration much higher, than physiologically needed on primary target (not suitable for repurposing?)	(Chen et al., 2017)
3hi2one-G4 	↑↑↑ $K_{ir}3.4$	Xenopus oocyte (TEVC): 12.74 μM HEK whole-cell: 5.15 μM	↑ $K_{ir}3.1/3.4$ × $K_{ir}3.2$ × $K_{ir}3.1/3.2$		(Cui et al., 2022)
Luteolin 	$K_{ir}4.1$	N/A	N/A	Natural compound	(Hong et al., 2023)
2-D08 	$K_{ir}4.1$	N/A ~25% current increase at 50 μM (−140 mV) 9 μM	N/A	Inhibitor of protein sumoylation	(Liu et al., 2025)

(Continues)

TABLE 8 (Continued)

Drug name	Target	EC_{50}	Selectivity	Comments	Ref.
CL-705G 	$K_{ir}6.2$-containing K_{ATP}		× $K_{ir}6.1$/SUR2B × $K_{ir}2.1$ × $K_{ir}3.1/3.4$ × $Na_v1.7$ (15 μM, ↓ 100 μM)	Putative binding site: At interface $K_{ir}6.2$/TM0 (SUR); no experimental validation	(Gando et al., 2023)

Abbreviation: AS1, Andersen·s syndrome type 1.

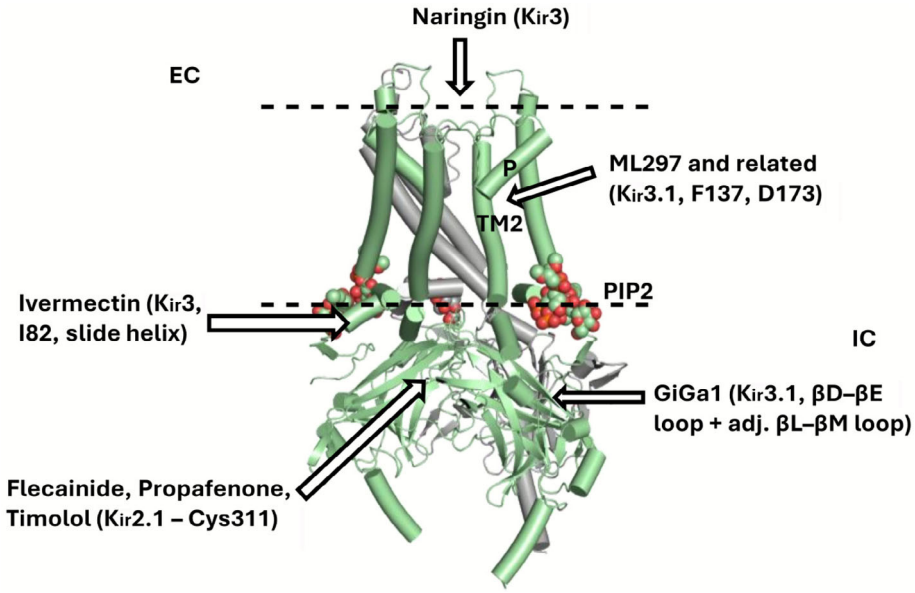


FIGURE 2 Overview of K_{IR} activators' binding sites. Structure generated with PyMOL. The transmembrane domain 2 (TM2), pore (P) domain, extracellular (EC) region, intracellular (IC) region, and PIP_2 (green and red spheres) at its binding site are indicated. Binding positions for several K_{IR} activators are shown: Naringin binds at the extracellular region of $K_{ir}3.x$ channels; ML297 and related compounds interact with residues F137 and D173 near the TM2 domain in $K_{ir}3.1$; ivermectin binds at residue I82 located at the slide helix of $K_{ir}3.x$; flecainide, GiGA1 interacts with the βD-βE loop and adjacent βL-βM loop in $K_{ir}3.1$; propafenone and timolol interact with C311 at the intercellular region of $K_{ir}2.1$.

selectivity for $K_{ir}2.1$ channels without blocking other ion channels like hERG or $Na_v1.5$ (propafenone prime target), making it a promising candidate for further development (Li et al., 2025).

High-throughput screening: Advances in screening technologies have enabled the identification of highly selective, potent small-molecule activators targeting $K_{ir}3$ channels, such as GAT1508 (Xu et al., 2020). These efforts have yielded compounds with varying degrees of selectivity and potency, but many still face challenges related to ADMET profiles and clinical translation.

The following subsections will explore specific examples of K_{IR} activators, their mechanisms of action and their potential therapeutic applications.

3.2.1 | $K_{ir}2.x$ subfamily

It was found that flecainide, propafenone and timolol all interact with Cys311 of $K_{ir}2.1$-generated homotetramers, decreasing the channels' affinity for polyamines and increasing the corresponding outward component of inward rectifier current (Figure 2) (Caballero et al., 2010; Gómez et al., 2014). Interestingly, flecainide incubation increases $K_{ir}2.1$ channel membrane expression and can rescue the Andersen disease mutant R67W, which exhibits a dominant-negative effect and loss-of-function, when expressed in CHO cells. Despite these promising *in vitro* data, a recent preprint reports that out of 53 Andersen's syndrome type 1 patients only 54% responded partially to flecainide and ventricular arrhythmia was reduced only in 23% of patients. Of note, several mutations, including R67W, showed an increase in rotor incidence at baseline when flecainide was given, revealing a proarrhythmic effect of the drug, severely limiting the usefulness of the drug for AS patients (Cruz et al., 2024, a https://doi.org/10.1101/2024.12.10.24318629). Similar mixed results were also observed for another Class-Ic-antiarrhythmic drug, propafenone, which was completely ineffective in 23% of cases with Andersen's syndrome type 1, suggesting that mutation-specific therapies are needed and that off-target effects of these multiple-ion channel blocking drugs limit their usefulness to a few patients. Thus, a recent medicinal chemistry and manual patch clamp screening approach has

been applied to obtain more potent and specific activators, like the propafenone analogue GPV0057 (Li et al., 2025). Importantly, GPV0057 has been shown not to block rapid delayed rectifier potassium current (I_{Kr}) at concentrations below 0.5 μmol L^{-1} nor $Na_v1.5$ current below 1 μmol L^{-1}, and action potential duration was not affected at similar concentrations in human-induced pluripotent stem cell–derived cardiomyocytes (hiPSC-CMC).

The endogenous neurosteroid **pregnenolone sulfate** selectively and reversibly potentiates $K_{ir}2.3$ channels, but not other K_{IR} subtypes, suggesting subtype-specific modulation. This effect appears extracellular, concentration-dependent and may extend to $K_{ir}2.3$-containing heterotetramers, with reported half-maximal effects in the low micromolar range. Surprisingly, none of the related neurosteroids had any effect on $K_{ir}2.3$, suggesting a highly specific mechanism, but details about binding site and structural basis of modulation remain unknown (Kobayashi et al., 2009).

Aminophylline, an approved bronchodilator, used for the treatment of chronic obstructive pulmonary disease and of severe asthma attacks, has been shown to induce both inhibition and, to a lesser extend activation of inward rectifier potassium current (I_{K1}) in individual cells, which is known to prolong and shorten, respectively, the duration of action potential (AP) and QT interval. Both effects can lead to various types of arrhythmias, especially in the presence of additional risk factors. The observed I_{K1} changes were induced at clinically relevant concentrations of aminophylline and thus might contribute to arrhythmogenesis related to the use of this bronchodilator in clinical medicine (Ramalho et al., 2022). However, no defined EC_{50} values or structural binding site have been reported.

3.2.2 | $K_{ir}3.x$ (GIRK) subfamily

Naringin, a bioflavonoid from grapefruit, has also been shown to activate GIRK channels (Yow et al., 2011). It has been shown to significantly activate neuronal GIRKs (GIRK1/2, 1/3, 3/4) in the range of 1 to 5 μmol L^{-1}. Naringin is metabolized to **naringenin**, yet it remains in the plasma for hours reaches maximum at 2 h after a single administration, decreases to 50% 3 h later (Bai et al., 2020). Importantly, the drug crosses the blood-brain barrier, building up to 900 ng·$g^{-1}$of brain tissue after a single administration, corresponding to ∼3.6 μmol L^{-1} (Zhang et al., 2022). Thus, naringin might be an interesting candidate as GIRK opener for human use.

Interestingly, the binding site is suggested to be on the extracellular side of the channel, overlapping with the bee toxin **tertiapin-Q** (Figure 2). The activation mechanism, although not understood in detail, has been shown to be independent of $G_{\beta\gamma}$ (Yow et al., 2011).

Secondly, following the establishment of specific high-throughput screening platforms such as automatic patch clamp electrophysiology, fluorophore-based membrane potential measurements or ion (**rubidium**, thallium) flux assays, to name a few (reviewed in Walsh, 2020), large small compound libraries have been screened for activation and inhibition of K_{IR} channel activity. Kaufmann et al. (2013) reported the discovery of a potent $K_{ir}3.1/K_{ir}3.x$ channel activator, named ML297 (VU0456810, CID 56642816), using the thallium flux assay. This and subsequent work established molecular mechanisms and demonstrated that its activation mechanism depends on PIP_2 and the presence of F137 and D173 residues in the $K_{ir}3.1$ protein (Figure 2) (Wydeven et al., 2014). ML297 preferentially activates the GIRK1/GIRK2 heterotetramers, compared with GIRK1/GIRK4 and is inactive in the potassium channels GIRK2/GIRK3, $K_{ir}2.1$, **$K_v7.4$** and hERG (Days et al., 2010).

Mechanistically, the activator has been shown to depend on PIP_2 but to be independent of G-protein coupling. Two residues in the GIRK1 subunit, F137 and D173, have been shown to be critical determinants for selective interaction. However, analysis of AlphaFold models and homology models of GIRK1/2 (as experimental 3D structures containing GIRK1 subunits are still lacking) reveals that residue F137 in the pore helix is not solvent accessible, when considering current 3D structures of $K_{ir}3.x$, only D173 (corresponding to the rectification controller position in TM2) appears accessible, suggesting an allosteric or otherwise unclear mechanism of action, which will likely require determination of high-resolution structures of the activator-bound channel state.

Encouragingly, ML297 exhibits anxiolytic effects without inducing sedation or reward-related behaviours. Notably, these anxiolytic effects are absent in GIRK1-deficient mice, underscoring the subunits essential role in mediating the compounds behavioural impact (Wydeven et al., 2014).

Given the promising features of this K_{IR} opener, Wen et al. (2014), performed a comprehensive structure–activity relationship (SAR) study starting from ML297, which identified several 'molecular switches' capable of altering the compound pharmacological activity, from activation to inhibition, as well as their selectivity between GIRK1/2 and GIRK1/4 channels. All compounds remained inactive on GIRK channels lacking GIRK1, highlighting the importance of this subunit for drug interactions. Generally, the structure–activity relationship proved rather complex, with small structural changes leading to significant shifts in both activity type and channel selectivity.

Given the suboptimal pharmacokinetic properties and modest selectivity of ML297 and derivatives for $K_{ir}3.1/3.2$ relative to $K_{ir}3.1/3.4$ channels, further synthesis efforts led to the development of VU0810464, a non-urea compound, which activates $K_{ir}3.1/3.2$ channels with nanomolar potency and displays improved selectivity for neuronal $K_{ir}3$ channels, with improved brain penetration (Vo et al., 2019). Intriguingly, this activator, although reducing stress-induced hyperthermia in mice, was ineffective to decrease anxiety-related behaviour as shown previously for ML297.

Interestingly, photoswitchable agonists (light-operated GIRK channel openers [LOGOs]) were developed based on ML297 and other GIRK1 modulators, to enable optical control of neuronal activity using light (Barber et al., 2016).

In 2020, a bromo-thiophene substituted derivative of ML297 was reported, named GAT1508, which has full specificity for GIRK1/2 over GIRK1/4 subunits, which is crucial in terms of cardiac safety profile (Xu et al., 2020). By combining electrophysiology, homology modelling, docking and molecular dynamics simulations, the authors

suggest that this activator binds to the same region as ML297 and interacts with multiple phenylalanines through π-stacking, stabilizing its aromatic structure. One end connects to the key pore-helix phenylalanine F137, whereas the other end engages another **phenylalanine**, which in turn allows a nearby tyrosine to shift its contact from the pore helix to the M2 helix aspartate D173. These interaction changes propagate through the channel structure, likely involving the slide helix and N-terminus, to enhance PIP_2 sensitivity and promote channel opening. The compound efficacy appears to depend on an intact or at least partially functional PIP_2 binding interface, as shown by mutagenesis. Brain-slice electrophysiology demonstrated that subthreshold concentrations of GAT1508 directly activate GIRK currents in the basolateral amygdala and potentiate **baclofen**-induced currents. Importantly, the activator shows promise as pharmacotherapy for post-traumatic stress disorder, by effectively extinguishing conditioned fear in rodents, without exhibiting behavioural or cardiac side effects (Xu et al., 2020).

Virtual screening approaches based on a known small molecule pocket have been successful in GIRK channels, which led to the discovery of GiGA1, a GIRK1-specific modulator through virtual screening against the alcohol pocket in GIRK2 (Y. Zhao et al., 2020). Similar to ML297, the activation mode of this small molecule is G protein independent, does not alter inward rectification of GIRK1/GIRK2 and exhibits a preference for the activation of GIRK1/GIRK2 channels, compared with GIRK1/GIRK4 or GIRK1/GIRK3. However, the binding site is located in the cytoplasmic domain (Figure 2). A relatively narrow pocket at the interface between two subunits is formed by the N-terminal domain, the βD–βE sheets from one subunit and the βL–β M sheets from the adjacent subunit and was originally identified in a cytoplasmatic domain X-ray structure of $K_{ir}2.1$ bound to an alcohol molecule (Pegan et al., 2005). Interestingly, GiGA1 has very fast activation and deactivation rates in the order of 2–s, whereas ML297 has much slower kinetics, with off-rates of t1/2≈20s (Y. Zhao et al., 2021).

GiGA1 has been shown to reduce neuronal excitability and seizure severity in preclinical models, showing promise for acute neurological conditions. Its rapid metabolism may help limit side effects; however, sedation has been observed, at high doses, potentially limiting more long-term treatments.

These selective activators are now being used to further decipher the role of these channels in normal and abnormal physiology (reviewed in Nguyen et al., 2024). A comprehensive review for GIRK-specific activators can be found here: Zhao et al., (2021).

In 2017, a study by Chen et al. (2017) reported that the approved antiparasitic drug **ivermectin** activates $K_{ir}3$ channels in a PIP_2-dependent manner but acts independently of G subunits βγ subunits. Residue I82 in the slide helix was identified as essential for activation.

In 2022, Cui et al. (2022) reported the discovery of a highly selective small-molecule activator targeting GIRK4 homotetrameric channels. 3hi2one-G4 (3-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]-3-hydroxy-1-(1-naphthylmethyl)-1,3-dihydro-2H-indol-2-one), as it is named, is proposed to bind to TM helices 1 and 2, as well as the slide helix, near the PIP_2 binding site, activating the channels via strengthening PIP_2 interactions. The drug is reported not to activate GIRK2, GIRK1/2 or GIRK1/4 channels. A major determinant for this isoform specificity was found at position L77.

3.2.3 | $K_{ir}4.1$-containing channels

Chronic treatment with antiepileptic drugs **valproate**, **phenytoin**, **phenobarbital** and **ethosuximide** has been reported to increase astrocytic $K_{ir}4.1$ expression (Mukai et al., 2018), but this likely reflects indirect transcriptional or trafficking effects rather than direct modulation of channel gating. More recently, two studies have provided evidence for direct pharmacological enhancement of $K_{ir}4.1$ activity. Hong et al. (2023) showed that the natural compound luteolin increases $K_{ir}4.1$-mediated currents in NG2 glia and promotes remyelination after ischemic injury, although the underlying mechanism remains unclear. In addition, M. Liu et al. (2025) identified the synthetic molecule 2-D08 as a potent $K_{ir}4.1$ potentiator in oligodendroglial cells, demonstrating improved myelin repair in models of multiple sclerosis. Both activators enhance $K_{ir}4.1$ currents at low micromolar concentrations in whole-cell recordings, but the exact binding sites and structural mechanisms are not yet resolved. Together, these findings establish $K_{ir}4.1$ as a pharmacologically tractable target and highlight the potential of $K_{ir}4.1$ activation in CNS repair.

3.2.4 | $K_{ir}6.x$-containing channels

In contrast to other K_{IR} subfamilies, the pharmacology of $K_{ir}6.x$-containing KATP channels are dominated by ligands that bind to the SUR1/SUR2 regulatory subunits, such as **diazoxide**, **pinacidil**, **nicorandil** and related Potassium Channel Openers (KCOs). These compounds modulate $K_{ir}6.x$ activity indirectly through nucleotide-binding domains and MgADP-dependent conformational coupling within SUR, rather than by interacting with the $K_{ir}6$ pore itself. Because the present review focuses on pore-directed K_{IR} activators, readers are referred to the recent comprehensive K_{ATP} review for detailed coverage of SUR-targeting openers (Martin et al., 2023).

A recent study (Gando et al., 2023) reports a novel activator, CL-705G, which is a potent and selective opener of $K_{ir}6.2$-containing K_{ATP} channels, with an EC_{50} of approximately 9 μmol L^{-1}. It activates $K_{ir}6.2$/SUR2A channels without affecting $K_{ir}6.1$/SUR2B or other K_{ir} channels. The drug was shown to activate $K_{ir}6.2\Delta36$ in the presence of SUR2A but not when expressed alone, indicating that its activity is dependent on the presence of the SUR subunit. The putative binding site was reported at the interface between the $K_{ir}6.2$ subunit and TMD0. Of note, the compound was still able to activate $K_{ir}6.2$/SUR2A channels after PIP_2 depletion, suggesting that this drug might be able to bypass PIP_2 effects and stabilize an alternative open conformation at the $K_{ir}6.2$–SUR interface.

To the best of our knowledge, no K_{IR} activator has been reported to date for the $K_{ir}1.1$, $K_{ir}4.1$/$K_{ir}5.1$ heterotetramers or $K_{ir}7.1$

subfamilies, despite their critical roles in pathophysiological processes. This lack of activators underscores a significant gap in the field and highlights the urgent need for further research. Encouragingly, high-throughput screening has been successful in identifying inhibitors for channels such as $K_{ir}1.1$, suggesting that similar approaches could be applied to develop K_{IR} activators.

Moreover, insights from structure–activity relationship studies in $K_{ir}3$ channels have demonstrated the feasibility of designing molecular switches—structural modifications in small molecules that can convert inhibitors into activators and vice versa (Wen et al., 2014). Recent GIRK studies (Jeremic et al., 2021; Luo et al., 2022) further underscore the mechanistic diversity of $K_{ir}3$ gating and highlight how subtle structural differences modulate PIP_2-dependent activation. These findings provide a valuable framework for rational drug design. Together, these findings suggest that similar strategies could guide the development of subtype-specific activators for $K_{ir}1.1$ and $K_{ir}4.1/K_{ir}5.1$ heterotetramers for which no direct activators are currently known. Likewise, the atypical inward rectifier $K_{ir}7.1$, characterized by unusually low single-channel conductance, weak inward rectification and comparatively low apparent PIP_2 affinity, has no endogenous or synthetic small-molecule activators identified to date.

For a detailed overview of $K_{ir}7.1$ structure and physiology, readers are referred to a recent review by Hernández et al. (2023).

Addressing these unmet needs has the potential to unlock new therapeutic opportunities for diseases associated with these K_{ir} subfamilies.

4 | GAPS TOWARDS CLINICAL STUDIES

Despite progress in the identification of small-molecule activators, particularly for $K_{ir}3$ channels, significant gaps remain in their preclinical characterization and translational potential. A key question is whether agonists can bypass impaired PIP_2 binding and directly promote channel opening in conditions such as Bartter's syndrome, Andersen's syndrome, EAST/SeSAME syndromes, congenital hyperinsulinism or snowflake vitreoretinal degeneration. To date, almost all activators described in literature so far, including ML297 and VU0810464, are dependent on PIP_2 for their mechanism of action, limiting their utility in cases where PIP_2-channel interactions are severely disrupted. This limitation highlights the broader challenge across the K_{IR} family. PIP_2 remains the dominant gating cofactor for all K_{IR} channels, yet subtype-specific differences in PIP_2 affinity and coupling mechanisms remain poorly understood. A detailed mechanistic framework for this lipid-dependent gating has recently been established (Zangerl-Plessl et al., 2025), providing a structural basis for how PIP_2 coupling drives conformational opening and underscoring the challenge of developing truly PIP_2-independent activators.

For conditions involving complete loss of channel expression or trafficking defects, such as severe loss-of-function mutations, K_{IR} activators are unlikely to provide therapeutic benefit.

In addition to mechanistic challenges, the preclinical evaluation of existing K_{IR} activators remains incomplete. Although compounds like ML297 and VU0810464 have undergone limited *in vivo* pharmacokinetics (PK) and drug metabolism and pharmacokinetics (DMPK) evaluations, comprehensive profiling, including full metabolic pathways, long-term tolerability studies and detailed pharmacokinetic modelling has not been conducted. For example, such studies have not even been initiated for promising compounds like GPV0057. Addressing these gaps is critical for advancing these tool compounds towards clinical development.

Besides mutation induced loss-of-function of K_{IR} channel activity, disease-associated remodelling may also reduce inward rectifier current, for example, in heart failure (Berry et al., 2019; Klein et al., 2017). Given the pleiotropic expression patterns of most K_{IR}s, it could be anticipated that normalizing K_{IR} function in the affected organ, for example, heart, by a specific K_{IR} activator may still cause adverse effects by increasing the same current in other organs and tissues not primarily targeted for therapy.

Finally, to better understand the translational potential of known K_{IR} activators, their chemical structures and ADMET liabilities must be systematically evaluated. Leveraging publicly available cheminformatics tools and general medicinal chemistry principles could provide a roadmap for optimizing these compounds. Looking forward, the most pressing needs include (i) identifying druggable K_{IR} conformational states, (ii) mapping activator binding sites with structural resolution and (iii), developing subtype-selective modulators that account for distinct PIP_2-coupling mechanisms across the K_{IR} family.

Addressing these gaps will be essential to unlock the therapeutic potential of K_{IR} activators and to translate promising preclinical findings into clinical success.

4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2025 (Alexander et al., 2025).

AUTHOR CONTRIBUTIONS

Anna Stary-Weinzinger: Writing—original draft (lead); writing—review and editing (lead). **Fabian Kaiser:** Writing—original draft (equal); writing—review and editing (equal). **Marcel A. G. van der Heyden:** Writing—review and editing (equal). **Saïd Bendahhou:** Writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

A.S.W., F.K. and S.B. declare no conflicts of interest. M.H. is a consulting editor for Research Integrity for the British Journal of Pharmacology.

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