Published in final edited form as:

Expert Opin Ther Pat. 2010 December ; 20(12): 1759–1765. doi:10.1517/13543776.2010.528392.

Spiro azepane-oxazolidinones as Kv1.3 potassium channel blockers - WO2010066840

Heike Wulff

University of California, Department of Pharmacology, 451 Health Sciences Drive, GBSF 3502, Davis, CA 95616, USA, Tel: +1 530 754 6135; hwulff@ucdavis.edu

Abstract

This article evaluates a patent application from Solvay Pharmaceuticals, which claims spiro azepane-oxazolidinones as novel blockers of the voltage-gated potassium channel Kv1.3 for the treatment of diabetes, psoriasis, obesity, transplant rejection and T-cell mediated autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. The patent describes a new chemotype of Kv1.3 blockers and thus illustrates the growing interest of the pharmaceutical industry in Kv1.3 as a target of immunosuppression and metabolic disorders. This article briefly summarizes the chemistry and biological data provided in the patent and then compares the new compounds to Kv1.3 blockers previously disclosed by both academia and pharmaceutical companies.

1. Introduction

The patent application from Solvay Pharmaceuticals, which after its acquisition by Abbott is now presumably held by Abbott, claims spiro azepane-oxazolidinones as novel Kv1.3 blockers for the treatment of diabetes, psoriasis, obesity, transplant rejection and T-cell mediated autoimmune diseases such as rheumatoid arthritis and multiple sclerosis. The patent itself only contains four lines of *Background* stating that other companies and academic institutions previously disclosed Kv1.3 blockers and provides no further rationale for why Kv1.3 blockers might be useful for the diseases named in the abstract and the claims. It is therefore left to the reader to search for primary literature and review articles to obtain background information about Kv1.3.

Kv1.3 is a voltage-gated potassium channel that is expressed in T cells [1,2], B cells [3], macrophages [4,5] osteoclasts [6], platelets [7], microglia [8,9], adipocytes [10], oligodendrocytes [11], and the olfactory bulb [12,13] and has been proposed as a target for immunosuppression since its initial description in human T cells in 1984 [1,2,14]. Kv1.3 blockers are assumed to exert their immunosuppressive effect by depolarizing the T cell membrane [15] and thus indirectly inhibiting Ca^{2+} entry through the calcium-release activated Ca^{2+} (CRAC) channel [14], which consists of the ER Ca^{2+} -sensor STIM1 and the pore forming protein Orai1 [16–19]. Kv1.3 blockers thus inhibit T cell Ca^{2+} signaling and NFAT translocation [20] similar to the calcineurin inhibitors cyclosporine and FK506 and were therefore initially regarded as general immunosuppressants in the 1990s [15,21]. However, based on the more recent finding that Kv1.3 blockers preferentially inhibit the Ca^{2+} -signaling, proliferation and *in vivo* migration of CCR7[−] effector memory T cells [22–24] while having little effect on naïve and CCR7⁺ central memory T cells, Kv1.3 blockers are now rather viewed as immunomodulators for the treatment of T-cell mediated autoimmune diseases such as MS, type-1 diabetes, rheumatoid arthritis (RA) and psoriasis [23,25–29], where effector memory T cells are involved in the pathogenesis. In support of this therapeutic hypothesis peptidic Kv1.3 blockers like margatoxin, kaliotoxin or ShK derivatives have been shown to prevent delayed-type hypersensitivity (DTH) in rats [24,30] and mini-pigs [31], to inhibit bone

resorption in experimental periodontal disease [32] and to treat pristane-induced arthritis [23] as well as adoptive-transfer [30,33] and chronic-relapsing [23,24] experimental autoimmune encephalomyelitis in rats. Similar promising observations have been made with small molecule Kv1.3 blockers like correolide, PAP-1 or Psora-4, which have been reported to prevent DTH [34,35], allergic contact dermatitis [36], spontaneous autoimmune diabetes in diabetes-prone Biobreeding Worchester rats [23] or anti-glomerular basement membrane glomerulonephritis [37] in rats. Kv1.3 was recently further corroborated as a target for immunosuppression by the finding that clofazimine, a drug that is marketed as Lamprene® by Novartis and which has been used for leprosy, pustular psoriasis, skin graft-versus-host-disease and discoid lupus erythematosus since the 1960s, inhibits Kv1.3 with an IC₅₀ of 300 nM and prevents the rejection of transplanted human foreskin in immunodeficient mice reconstituted with human T cells [38]. In severe combined immunodeficient (SCID) mice injection of ShK into transplanted skin grafts from psoriasis patients was further observed to reduce inflammatory responses in a subset of responding grafts [39].

Based on experiments with Kv1.3^{-/-} mice, Kv1.3 has further been suggested as a target for the treatment of type-2 diabetes and obesity [40]. Kv1.3^{-/-} mice have been reported to be more insulin sensitive and to gain less weight on a high-fat diet than wild-type littermates. The mechanism that has been proposed for this observation is that Kv1.3 blockade or genetic deletion in adipose tissue and skeletal muscle facilitates the translocation of the glucose transporter GLUT4 to the plasma membrane [41]. Deletion of Kv1.3 has further been found to reduce adiposity and increase lifespan in a genetic model of obesity. Double Kv1.3 and melanocortin-4 receptor (MC4R) knockout mice exhibited a lower bodyweight, lived longer and showed increased reproductive success compared to MC4R^{-/-} mice [42].

2. Chemistry

The 1-oxa-3,8-diazaspiro[4.6]undecan-2-ones disclosed in the invention were synthesized starting from hexahydro(1*H*)-azepin-4-one (**1** in Scheme 1) by first protecting its amino group and then epoxidizing the keto function with trimethyl sulfoxonium iodide in the presence of a strong base such as sodium hydride. The resulting spiro-epoxides (**3**) were aminolysed with (R)- or (S)-1-phenylethyl amines (**4**) and subsequently ring-closed to a [4.6]diazaspiroundecane spirocycle (**6**) using the carbonylating agent carbonyldiimidazole (CDI). Following removal of the protecting *tert*-Boc group the resulting secondary amine (**7**) was then acetylated with aromatic acid chlorides (**8**) to render the target compounds (**9–40**). Using this method 31 azepane-oxazolidinones were prepared either as racemic mixtures or as optically pure compounds. Absolute configurations were determined by vibrational circular dichroism.

3. Biology and action

Apart from rather lengthy and often tedious definitions of general terms such as “dose”, “inhibit”, or “treatment” the patent only contains a single table of biological data showing percentage of rubidium efflux inhibition from CHO cells stably expressing Kv1.3. All compounds were tested at a single dose of 10 µM. While the majority of compounds produced between 40–85% inhibition and therefore probably have IC₅₀ values between 2 and 20 µM, three compounds showed approximately 100% inhibition and could potentially have nanomolar IC₅₀ values (see Figure 1 for structures). However, since no standard Kv1.3 blockers such as margatoxin, verapamil or Psora-4 were tested in the assay it is hard to judge the quality of the data. In cases where two enantiomers or even all four enantiomers of a diastomer pair were examined, only very minor differences in Kv1.3 blocking activity were observed (see for example **29** and **32** in Figure 1) demonstrating that stereochemistry does not influence the Kv1.3 blocking activity of the azepane-oxazolidinones.

4. Expert opinion

The current invention is the second application from Solvay Pharmaceuticals for Kv1.3 blockers. A previous patent from 2007 had claimed compounds with mixed Kv1.3 inhibiting, CB₁ antagonizing and K_{ATP} channel opening properties for the prevention and treatment of type-1 and type-2 diabetes [43]. The most potent compound from this previous patent (Figure 2) exhibited a similar potency (96% block of Kv1.3 at 10 μ M) as the presently disclosed compounds but does not seem to have been developed further.

The current invention is primarily of interest because it describes a new chemotype of Kv1.3 blockers and is a demonstration of the growing interest of the pharmaceutical industry in Kv1.3 as a target for immunosuppression and type-2 diabetes. Solvay Pharmaceuticals, or now presumably Abbott, is thus joining the ranks of Pfizer and Merck, who have been pursuing Kv1.3 for immunosuppression since the early 1990s and identified dihydroquinoline, piperidine, nortriterpene- or benzamide type Kv1.3 blockers exemplified by CP-339818 [44–46], UK-78,282 [47,48], correolide [34,49,50,51] and trans-*N*-propyl-carbamoyloxy-PAC [52,53] (Figure 2). Other, later identified small molecule Kv1.3 blockers are the phenoxyalkoxypsoralens from the University of California exemplified by PAP-1 [35], a series of related khellin and khellinone derived compounds from a collaboration between the Walter and Eliza Hall Institute (WEHI) of Medical Research in Australia and Bionomics [54–58] and the leprosy drug clofazimine [38]. In addition to these small molecules approaches other companies are targeting Kv1.3 with venom-derived peptides. Airmid and Kineta Inc. have an ShK derivative in preclinical development for MS, while Amgen Inc. is making efforts to prolong the short half-life of peptides like ShK or the scorpion toxin OSK1 by conjugating them to Fc antibody fragments [59]. While peptides targeting the outer vestibule of Kv1.3 can of course exhibit exquisite Kv1 channel subtype specificity and can be engineered to be highly selective for Kv1.3 as in the case of ShK-L5 [30] or [K₁₆,D₂₀]-OSK1 [60], achieving selectivity for small molecules, which typically bind in the inner pore or the water filled internal cavity of the channel [61,62], has been a tremendous challenge for both industry and academia. In addition to avoiding cross reactivity to HERG (Kv11.1) and neuronal sodium channels (which was a problem for the early Pfizer compounds), a small molecule Kv1.3 blocker should also be selective over the very closely related Kv1-family channels Kv1.1, Kv1.2, Kv1.4, Kv1.5, Kv1.6 and Kv1.7, which display a very high degree of homology in the intracellular part of the S5-P-S6 region, where most of the small molecule blockers bind. Correolide for example affects all Kv1-family channels with equivalent affinity, and by blocking Kv1.1 channels increased the peristaltic activity of the gastrointestinal tract [63,64]. So far, the only small molecule Kv1.3 blockers that exhibit degrees of selectivity that seem acceptable for development are PAP-1, which exhibits 23-fold selectivity over the Kv1.5 and 33- to 125-fold selectivity over the rest of the Kv1-family channels [35], and several of the Bionomics compounds like the example shown in Figure 2, which has been reported to exhibit 37-fold selectivity over Kv1.5 [58,65]. While PAP-1 is currently in preclinical development for psoriasis, Bionomics seems to be developing their compounds for multiple sclerosis, rheumatoid arthritis and psoriasis. Selectivity over Kv1.5 is of particular concern for Kv1.3 blockers because Kv1.5 underlies the ultra-rapid delayed rectifier in the human atrium and although the channel is hotly pursued as a target of the treatment of atrial fibrillation [62], an immunosuppressant or anti-obesity drug should ideally not affect Kv1.5. Since the selectivity of the Solvay Kv1.3 blockers has not been studied (or is not disclosed in the current invention) it is hard to judge whether any of the compounds are suitable for development. Before this can be evaluated the compounds of course also need to show efficacy *in vivo* and their toxicity and bioavailability needs to be determined.

Acknowledgments

Declaration of Interest

This work was supported by NIH American Recovery and Reinvestment Act funds (RO1 GM076063-04S1).

H Wulff has been working on Kv1.3 for 10 years, is an inventor on University of California patents claiming Kv1.3 blockers for immunosuppressants, and a scientific founder of Airmid LLC, a small biotech attempting to develop Kv1.3 blockers.

References

1. DeCoursey TE, Chandy KG, Gupta S, Cahalan MD. Voltage-gated K⁺ channels in human T lymphocytes: a role in mitogenesis? *Nature* 1984;307:465–468. [PubMed: 6320007]
2. Matteson DR, Deutsch CK. channels in T lymphocytes: a patch clamp study using monoclonal antibody adhesion. *Nature* 1984;307:468–471. [PubMed: 6320008]
3. Wulff H, Knaus HG, Pennington M, Chandy KG. K⁺ channel expression during B-cell differentiation: implications for immunomodulation and autoimmunity. *J Immunol* 2004;173:776–786. [PubMed: 15240664]
4. Mackenzie AB, Chirakkal H, North RA. Kv1.3 potassium channels in human alveolar macrophages. *Am J Physiol Lung Cell Mol Physiol* 2003;285:L862–L868. [PubMed: 12909584]
5. Vicente R, Escalada A, Coma M, Fuster G, Sanchez-Tillo E, Lopez-Iglesias C, et al. Differential Voltage-dependent K⁺ Channel Responses during Proliferation and Activation in Macrophages. *J Biol Chem* 2003;278(47):46307–46320. [PubMed: 12923194]
6. Arkett SA, Dixon J, Yang JN, Sakai DD, Minkin C, Sims SM. Mammalian osteoclasts express a transient potassium channel with properties of Kv1.3. *Receptors Channels* 1994;2:281–293. [PubMed: 7536610]
7. Maruyama Y. A patch-clamp study of mammalian platelets and their voltage-gated potassium current. *J Physiol* 1987;391:467–485. [PubMed: 2451010]
8. Schlichter LC, Sakellaropoulos G, Ballyk B, Pennefather PS, Phipps DJ. Properties of K⁺ and Cl[−] channels and their involvement in proliferation of rat microglial cells. *Glia* 1996;17:225–236. [PubMed: 8840164]
9. Khanna R, Roy L, Zhu X, Schlichter LC. K⁺ channels and the microglial respiratory burst. *Am J Physiol Cell Physiol* 2001;280:C796–C806. [PubMed: 11245596]
10. Pappone PA, Ortiz-Miranda SI. Blockers of voltage-gated K channels inhibit proliferation of cultured brown fat cells. *Am J Physiol* 1993;264:C1014–C1019. [PubMed: 8476010]
11. Chittajallu R, Chen Y, Wang H, Yuan X, Ghiani CA, Heckman T, et al. Regulation of Kv1 subunit expression in oligodendrocyte progenitor cells and their role in G1/S phase progression of the cell cycle. *Proc Natl Acad Sci USA* 2002;99:2350–2355. [PubMed: 11854528]
12. Fadool DA, Levitan IB. Modulation of olfactory bulb neuron potassium current by tyrosine phosphorylation. *J Neurosci* 1998;18:6126–6137. [PubMed: 9698307]
13. Fadool DA, Tucker K, Perkins R, Fasciani G, Thompson RN, Parsons AD, et al. Kv1.3 channel gene-targeted deletion produces "Super-Smeller Mice" with altered glomeruli, interacting scaffolding proteins, and biophysics. *Neuron* 2004;41:389–404. [PubMed: 14766178]
14. Chandy KG, Wulff H, Beeton C, Pennington M, Gutman GA, Cahalan MD. Potassium channels as targets for specific immunomodulation. *Trends Pharmacol Sci* 2004;25:280–289. [PubMed: 15120495]
15. Lin CS, Boltz RC, Blake JT, Nguyen M, Talento A, Fischer PA, et al. Voltage-gated potassium channels regulate calcium-dependent pathways involved in human T lymphocyte activation. *J Exp Med* 1993;177:637–645. [PubMed: 7679705]
16. Zhang SL, Yu Y, Roos J, Kozak JA, Deerinck TJ, Ellisman MH, et al. STIM1 is a Ca²⁺ sensor that activates CRAC channels and migrates from the Ca²⁺ store to the plasma membrane. *Nature* 2005;437:902–905. [PubMed: 16208375]

17. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. *Nature* 2006;441:179–185. [PubMed: 16582901]
18. Vig M, Peinelt C, Beck A, Koomoa DL, Rabah D, Koblan-Huberson M, et al. CRACM1 is a plasma membrane protein essential for store-operated Ca²⁺ entry. *Science* 2006;312:1220–1223. [PubMed: 16645049]
19. Feske S. Calcium signalling in lymphocyte activation and disease. *Nat Rev Immunol* 2007;7:690–702. [PubMed: 17703229]
20. Cahalan MD, Chandy KG. The functional network of ion channels in T lymphocytes. *Immunol Rev* 2009;231:59–87. [PubMed: 19754890]
21. Cahalan MD, Chandy KG. Ion channels in the immune system as targets for immunosuppression. *Curr Opin Biotechnol* 1997;8:749–756. [PubMed: 9425667]
22. Wulff H, Calabresi PA, Allie R, Yun S, Pennington M, Beeton C, et al. The voltage-gated Kv1.3 K⁺ channel in effector memory T cells as new target for MS. *J Clin Invest* 2003;111:1703–1713. [PubMed: 12782673]
23. Beeton C, Wulff H, Standifer NE, Azam P, Mullen KM, Pennington MW, et al. Kv1.3 channels are a therapeutic target for T cell-mediated autoimmune diseases. *Proc Natl Acad Sci U S A* 2006;103:17414–17419. [PubMed: 17088564]
24. Matheu MP, Beeton C, Garcia A, Chi V, Rangaraju S, Safrina O, et al. Imaging of effector memory T cells during a delayed-type hypersensitivity reaction and suppression by Kv1.3 channel block. *Immunity* 2008;29:602–614. [PubMed: 18835197]
25. Markovic-Plese S, Cortese I, Wandering KP, McFarland HF, Martin R. CD4+CD28-costimulation-independent T cells in multiple sclerosis. *J Clin Invest* 2001;108:1185–1194. [PubMed: 11602626]
26. Viglietta V, Kent SC, Orban T, Hafler DA. GAD65-reactive T cells are activated in patients with autoimmune type 1a diabetes. *J Clin Invest* 2002;109:895–903. [PubMed: 11927616]
27. Kivisakk P, Mahad DJ, Callahan MK, Sikora K, Trebst C, Tucky B, et al. Expression of CCR7 in multiple sclerosis: Implications for CNS immunity. *Ann Neurol* 2004;55:627–638. [PubMed: 15122702]
28. Rus H, Pardo CA, Hu L, Darrah E, Cudrici C, Niculescu T, et al. The voltage-gated potassium channel Kv1.3 is highly expressed on inflammatory infiltrates in multiple sclerosis brain. *Proc Natl Acad Sci U S A* 2005;102:11094–11099. [PubMed: 16043714]
29. Beeton C, Chandy KG. Potassium channels, memory T cells and multiple sclerosis. *Neuroscientist* 2005;11:550–562. [PubMed: 16282596]
30. Beeton C, Pennington MW, Wulff H, Singh S, Nugent D, Crossley G, et al. Targeting effector memory T cells with a selective peptide inhibitor of Kv1.3 channels for therapy of autoimmune diseases. *Mol Pharmacol* 2005;67:1369–1381. [PubMed: 15665253]
31. Koo GC, Blake JT, Talento A, Nguyen M, Lin S, Sirotina A, et al. Blockade of the voltage-gated potassium channel Kv1.3 inhibits immune responses in vivo. *J Immunol* 1997;158:5120–5128. [PubMed: 9164927]
32. Valverde P, Kawai T, Taubman MA. Selective blockade of voltage-gated potassium channels reduces inflammatory bone resorption in experimental periodontal disease. *J Bone Miner Res* 2004;19:155–164. [PubMed: 14753747]
33. Beeton C, Wulff H, Barbaria J, Clot-Faybesse O, Pennington M, Bernard D, et al. Selective blockade of T lymphocyte K⁺ channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. *Proc Natl Acad Sci USA* 2001;98:13942–13947. [PubMed: 11717451]
34. Koo GC, Blake JT, Shah K, Staruch MJ, Dumont F, Wunderler D, et al. Correolide and derivatives are novel immunosuppressants blocking the lymphocyte Kv1.3 potassium channels. *Cell Immunol* 1999;197:99–107. [PubMed: 10607427]
35. Schmitz A, Sankaranarayanan A, Azam P, Schmidt-Lassen K, Homerick D, Hansel W, et al. Design of PAP-1, a selective small molecule Kv1.3 blocker, for the suppression of effector memory T Cells in autoimmune diseases. *Mol Pharmacol* 2005;68:1254–1270. [PubMed: 16099841]
36. Azam P, Sankaranarayanan A, Homerick D, Griffey S, Wulff H. Targeting effector memory T cells with the small molecule Kv1.3 blocker PAP-1 suppresses allergic contact dermatitis. *J Invest Dermatol* 2007;127:1419–1429. [PubMed: 17273162]

37. Hyodo T, Oda T, Kikuchi Y, Higashi K, Kushiya T, Yamamoto K, et al. Voltage-gated potassium channel Kv1.3 blocker as a potential treatment for rat anti-glomerular basement membrane glomerulonephritis. *Am J Physiol Renal Physiol*. 2010 Sep 1; Epub ahead of print.
38. Ren YR, Pan F, Parvez S, Fleig A, Chong CR, Xu J, et al. Clofazimine inhibits human Kv1.3 potassium channel by perturbing calcium oscillation in T lymphocytes. *PLoS ONE* 2008;3:e4009. [PubMed: 19104661]
39. Gilhar A, Bergman R, Assay B, Ullmann Y, Etzioni A. The beneficial effect of blocking Kv1.3 in the psoriasiform SCID mouse model. *J Invest Dermatol*. 2010 Aug 26; Epub ahead of print.
40. Xu J, Koni PA, Wang P, Li G, Kaczmarek L, Wu Y, et al. The voltage-gated potassium channel Kv1.3 regulates energy homeostasis and body weight. *Hum Mol Gen* 2003;12:551–559. [PubMed: 12588802]
41. Xu J, Wang P, Li Y, Li G, Kaczmarek LK, Wu Y, et al. The voltage-gated potassium channel Kv1.3 regulates peripheral insulin sensitivity. *Proc Natl Acad Sci USA* 2004;101:3112–3117. [PubMed: 14981264]
42. Tucker K, Overton JM, Fadool DA. Kv1.3 gene-targeted deletion alters longevity and reduces adiposity by increasing locomotion and metabolism in melanocortin-4 receptor-null mice. *Int J Obes (Lond)* 2008;32:1222–1232. [PubMed: 18542083]
43. Solvay Pharmaceuticals GMBH. Methods of using potassium channel inhibiting compounds WO2007020286 A2. 2007.
44. Michne W, Guiles J, Treasurywala A, Castonguay L, Weigelt C, Oconnor B, et al. Novel inhibitors of potassium ion channels on human T lymphocytes. *J Med Chem* 1995;38:1877–1883. [PubMed: 7540207]
45. Hill RJ, Grant AM, Volberg W, Rapp L, Faltynek C, Miller D, et al. WIN 17317-3: novel nonpeptide antagonist of voltage-activated K⁺ channels in human T lymphocytes. *Mol Pharmacol* 1995;48:98–104. [PubMed: 7542739]
46. Nguyen A, Kath JC, Hanson DC, Biggers MS, Canniff PC, Donovan CB, et al. Novel nonpeptide agents potentially block the C-type inactivated conformation of Kv1.3 and suppress T cell activation. *Mol Pharmacol* 1996;50:1672–1679. [PubMed: 8967992]
47. Burgess LE, Kock K, Cooper K, Biggers MS, Ramchandani M, Smitrovich JH, et al. The SAR of UK-78,282: a novel blocker of human T cell Kv1.3 potassium channels. *Bioorg & Med Chem Lett* 1997;7:1047–1052.
48. Hanson DC, Nguyen A, Mather RJ, Rauer H, Koch K, Burgess LE, et al. UK-78,282, a novel piperidine compound that potentially blocks the Kv1.3 voltage-gated potassium channel and inhibits human T cell activation. *Br J Pharmacol* 1999;126:1707–1716. [PubMed: 10372812]
49. Goetz MA, Hensens OD, Zink DL, Borris RP, Morales F, Tamayo-Castillo G, et al. Potent Nor-triterpenoid blockers of the voltage-gated potassium channel Kv1.3 from *Spachea correae*. *Tetrahedron Lett* 1998;39:2895–2898.
50. Felix JP, Bugianesi RM, Schmalhofer WA, Borris R, Goetz MA, Hensens OD, et al. Identification and biochemical characterization of a novel nortriterpene inhibitor of the human lymphocyte voltage-gated potassium channel, Kv1.3. *Biochemistry* 1999;38:4922–4930. [PubMed: 10213593]
51. Hanner M, Schmalhofer WA, Green B, Bordallo C, Liu J, Slaughter RS, et al. Binding of correolide to Kv1 family potassium channels. *J Biol Chem* 1999;274:25237–25244. [PubMed: 10464244]
52. Schmalhofer WA, Bao J, McManus OB, Green B, Matyskiela M, Wunderler D, et al. Identification of a new class of inhibitors of the voltage-gated potassium channel, Kv1.3, with immunosuppressant properties. *Biochemistry* 2002;18:7781–7794. [PubMed: 12056910]
53. Miao S, Bao J, Garcia ML, Goulet JL, Hong XJ, Kaczorowski G, et al. Benzamide derivatives as blockers of the Kv1.3 ion channel. *Bioorg Med Chem Lett* 2003;13:1161–1164. [PubMed: 12643934]
54. Baell JB, Gable RW, Harvey AJ, Toovey N, Herzog T, Hansel W, et al. Khellinone derivatives as blockers of the voltage-gated potassium channel Kv1.3: synthesis and immunosuppressive activity. *J Med Chem* 2004;47:2326–2336. [PubMed: 15084131]
55. Harvey AJ, Baell JB, Toovey N, Homerick D, Wulff H. A new class of blockers of the voltage-gated potassium channel Kv1.3 via modification of the 4- or 7-position of khellinone. *J Med Chem* 2006;49:1433–1441. [PubMed: 16480279]

56. Bionomics Limited, Australia. Novel benzofuran potassium channel blockers and uses thereof WO2008040057. 2008.
57. Bionomics Limited, Australia. Novel chromenone potassium channel blockers and uses thereof WO2008040058. 2008.
58. Bionomics Limited, Australia. Novel aryl potassium channel blockers and uses thereof WO2009043117. 2009.
59. Amgen. Fusion proteins of toxin peptides with linkers and IgG and their use as therapeutic agents WO2006116156. 2006.
60. Mouhat S, Visan V, Ananthakrishnan S, Wulff H, Andreotti N, Grissmer S, et al. K⁺ channel types targeted by synthetic OSK1, a toxin from *Orthochirus scrobiculosus* scorpion venom. *Biochem J* 2005;385:95–104. [PubMed: 15588251]
61. Wulff H, Zhorov BS. K⁺ channel modulators for the treatment of neurological disorders and autoimmune diseases. *Chem Rev* 2008;108:1744–1773. [PubMed: 18476673]
62. Wulff H, Castle NA, Pardo LA. Voltage-gated potassium channels as therapeutic targets. *Nat Rev Drug Discov* 2009;8:982–1001. [PubMed: 19949402]
63. Vianna-Jorge R, Oliveira C, Garcia M, Kaczorowski G, Suarez-Kurtz G. Correolide, a nor-triterpenoid blocker of shaker-type Kv1 channels elicits twitches in guinea-pig ileum by stimulating the enteric nervous system and enhancing neurotransmitter release. *Br J Pharmacol* 2000;131:772–778. [PubMed: 11030727]
64. Vianna-Jorge R, Oliveira CF, Garcia ML, Kaczorowski GJ, Suarez-Kurtz G. Shaker-type Kv1 channel blockers increase the peristaltic activity of guinea-pig ileum by stimulating acetylcholine and tachykinins release by the enteric nervous system. *Br J Pharmacol* 2003;138:57–62. [PubMed: 12522073]
65. Nguyen W, Howard BL, Neale DS, Thompson PE, White PJ, Wulff H, et al. Use of Kv1.3 blockers for inflammatory skin conditions. *Curr Med Chem* 2010;17:2882–2896. [PubMed: 20858170]

Figure 1.
Exemplary compounds and their Kv1.3 blocking activity in rubidium flux.

Figure 2.
Structures of Kv1.3 blockers.

Scheme 1.
General synthetic route.