

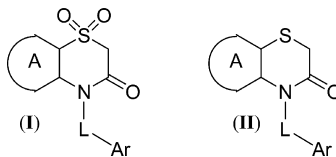
Fused Thiazin-3-ones as KCa3.1 Inhibitors

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Title:	Fused Thiazin-3-ones as KCa3.1 Inhibitors		
Patent Application Number:	WO2013191984	Publication date:	December 27th, 2013
Priority Application:	US61/662,632	Priority date:	June 21st, 2012
Inventors:	Burke, Michael J.; Mckibben, Bryan; Tschantz, Matt Aaron		
Assignee Company:	Boehringer Ingelheim International		
Disease Area:	Inflammatory disease	Biological Target:	KCa3.1
Summary:	The intermediate conductance calcium activated potassium channel KCa3.1, also known as KCNN4, SK4, IKCa1, IK1, and the Gardos channel, acts as a sensor for intracellular Ca^{2+} concentrations through its calmodulin domain (C-terminus). This channel serves to maintain a negative membrane potential through the efflux of potassium ions, which supports Ca^{2+} entry into cells. It is expressed in a variety of cells including, but not limited to, red blood cells, T-cells, B-cells, macrophages, mast cells, fibroblast, microglial cells, vascular smooth muscle cells, and epithelial cells. Cytokine production, proliferation, and migration of these cells are impacted by activation of this channel, and as such, disease associated with these processes may be impacted by compounds that modulate KCa3.1 activity. The present application discloses a series of fused thiazin-3-ones capable of blocking the KCa3.1 channel and composition useful for the treatment of disease associated with KCa3.1 activity.		

Important Compound Classes:



Definitions:

L is a bond or $-(\text{CH}_2)_n-$ wherein one or more methylene hydrogens is optionally replaced by C_{1-5} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, or C_{1-5} haloalkyl;

n is 1 to 3;

Ar is aryl or heteroaryl substituted independently by one or more halogen, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, or C_{1-6} haloalkylS(O) m -, and Ar is optionally further substituted by C_{1-6} alkyl;

m is 0, 1, 2;

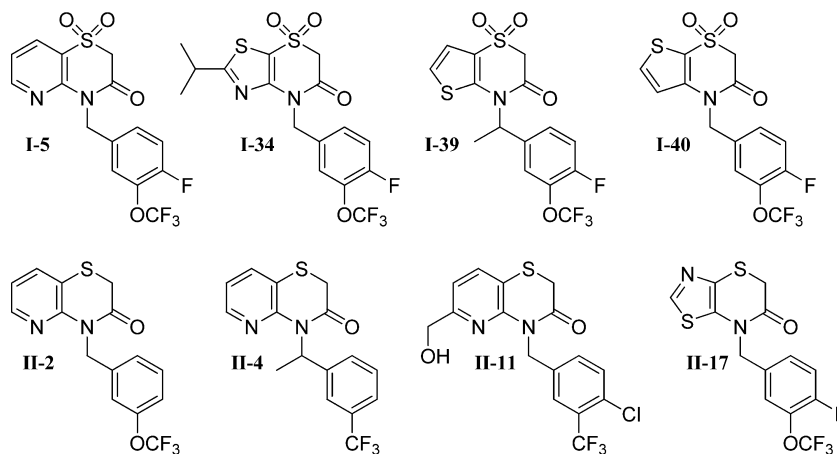
each R^1 , R^2 , and R^3 are independently chosen from hydrogen, halogen, C_{1-5} alkyl, C_{3-6} cycloalkyl, C_{1-5} alkyl-OH, $-\text{C}(\text{O})\text{OR}^4$, $-\text{C}(\text{O})\text{NR}^4\text{R}^4$, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-5} haloalkyl, $-\text{OR}^4$, $-\text{NR}^4\text{R}^4$, $-\text{CN}$, $-\text{SR}^4$, $-\text{S}(\text{O})_2\text{R}^4$, $-\text{S}(\text{O})_2\text{NR}^4\text{R}^4$, $-\text{NHC}(\text{O})\text{R}^4$, and $-\text{N}(\text{C}_{1-4}\text{alkyl})\text{C}(\text{O})\text{OR}^4$;

each R^4 is independently hydrogen or C_{1-6} alkyl.

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Key Structures:



Recent Review Articles:

Heike Wulff, H.; Castle, N. A. Therapeutic potential of KCa3.1 blockers: an overview of recent advances, and promising trends. *Expert Rev. Clin. Pharmacol.* **2010**, 3 (3), 385–396.

Chou, C. C.; Lunn, C. A.; Murgolo, N. J. KCa3.1: target and marker for cancer, autoimmune disorder and vascular inflammation? *Expert Rev. Mol. Diagn.*, **2008**, 8 (2), 179–187.

Biological Assay:

KCa3.1 thallium influx assay: HEK293 cells overexpressing human KCa3.1, FLIPR assay kit #R8154 (Molecular Devices), Hamamatsu 6000 platform.

Biological Data:

Entry	KCa3.1 IC ₅₀ (nM)	Entry	KCa3.1 IC ₅₀ (nM)
I-5	49	II-1	52
I-34	96	II-4	41
I-39	39	II-11	66
I-40	48	II-17	60

Claims:

26 Total claims

25 Composition of matter claims

1 Method of use claim directed toward the treatment of rheumatoid arthritis, psoriasis, atherosclerosis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, scleroderma, glomerulonephritis, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, graft versus host diseases, Alzheimer's disease, chronic kidney disease, type 1 and type 2 diabetes, osteoporosis, sickle cell disease, restenosis, periodontal disease, restenosis, renal fibrosis, lung fibrosis, and liver fibrosis.

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Notes

The authors declare no competing financial interest.