ACS Medicinal Chemistry Letters

Viewpoint

pubs.acs.org/acsmedchemlett

Derivatives of Heteroarylsulfonamides, Their Preparation, and Their Application in Human Therapy

Patent Highlight

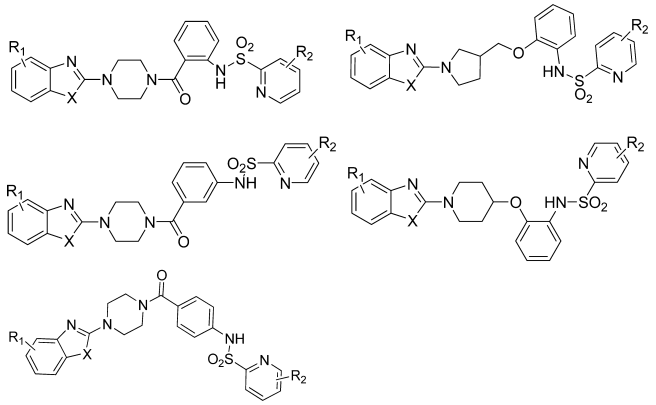
Benjamin Blass*

Temple University School of Pharmacy, 3307 North Broad Street, Philadelphia, Pennsylvania 19140, United States

Title:	Derivatives of Heteroarylsulfonamides, Their Preparation, and Their Application in Human therapy		
Patent/Patent Application Number:	WO2012/069503A1	**Publication Date:**	May 31, 2012
Priority Application:	FR1059634	**Priority Date:**	November 23, 2010
Inventors:	Dupont-Pas-Selaigue, Elisabeth; Le Roy, Isabelle; Pignier, Christophe		
Assignee Company:	Pierre Fabre Medicament		
Disease Area:	Cardiovascular Disease, Atrial Fibrillation	**Biological Target:**	Voltage Gated Potassium Channel $K_v1.5$

Summary: Voltage-gated potassium channels play a prominent role in excitable cells, particularly in the heart, where they are responsible for maintaining cardiac rhythm and cardiac repolarization. In heart rhythm disorders, such as atrial fibrillation, normal cardiac rhythm is interrupted by electrical reentry circuits, creating irregular electrical activity in the heart and asynchronous contractions of cardiac tissue. Nonselective blockade of multiple cardiac ion channels has been employed to decrease atrial fibrillation events by increasing the effective refractory period, but hERG-mediated side effects, including Torsade de pointes and sudden cardiac death, are known complications of nonselective channel blockade. This is primarily the result of the hERG channel's critical role in ventricular repolarization. The $K_v1.5$ channel, on the other hand, plays a critical role in repolarization of the atrial chamber of the heart but has no role in repolarization of the ventricular chamber. In addition, the $K_v1.5$ channel is not functionally expressed in the ventricular chamber. As such, it has been hypothesized that a compound with a high degree of selectivity for $K_v1.5$ over hERG should provide an effective treatment for atrial fibrillation, while decreasing hERG-related risks. This patent application discloses a series of heteroarylsulfonamides that are useful as $K_v1.5$ channel inhibitors for the treatment of atrial fibrillation.

Important Compound Classes:



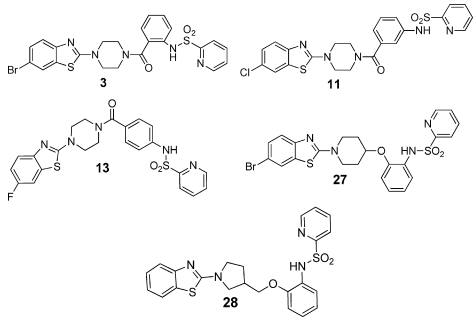
Definitions:

X = S, O

R_1 = H, halogen, CF_3, OCF_3, C1−C4 linear or branched alkyl, C1−C4 alkoxy

R_2 = H, methyl, methoxy, fluorine, chlorine

Key Structures:



Published: July 2, 2012

dx.doi.org/10.1021/ml3001598 | *ACS Med. Chem. Lett.* 2012, 3, 618−619

Recent Review Articles: Firth, A. L.; Yuan, J. X.-J. Antagonists of the $K_v1.5$ potassium channel. *Drugs Future* **2008**, *33* (1), 31−47.

Yang, Q.; Wang, X.; Du, L.; Li, M.; You, Q. Strategies for atrial fibrillation therapy: Focusing on IKur potassium channel. *Expert Opin. Ther. Pat.* **2007**, *17* (12), 1443−1456.

Biological Assay: $K_v1.5$ FLIPR using stably transfected HEK293 cells and the FLIPR potassium ion channel assay kit available from Molecular Devices.

Biological Data: Table 1: Exemplary $K_v1.5$ Inhibition Data

Example	% inhibition @10 μM	Example	% inhibition @10 μM
3	100	27	100
11	75.1	28	76
13	100		

AUTHOR INFORMATION

Corresponding Author

*Tel: 215-707-1085. E-mail: Benjamin.Blass@Temple.edu.

Notes

The authors declare no competing financial interest.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on July 2, 2012, with an erroneous structure label. The corrected version was reposted on July 27, 2012.