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PATENT HIGHLIGHT

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Inhibitors of the Renal Outer Medullary Potassium Channel

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Title:	Inhibitors of the renal outer medullary potassium channel		
Patent/Patent Application Number:	WO2015017305A1	**Publication date:**	Feb 5, 2015
Priority Application:	US 61/860,270	**Priority date:**	July 31, 2013
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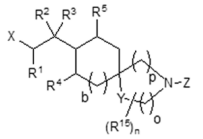
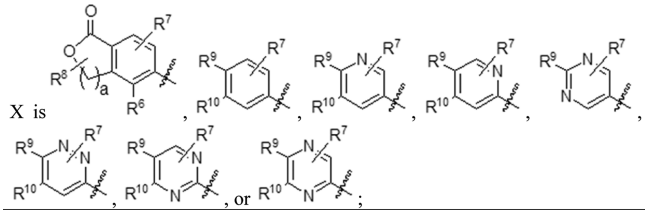
Inventors:	Tang, H.; Pio, B.; Jiang, J.; Pasternak, A.; Dong, S.; Ferguson, R. D., II; Guo, Z. Z.; Chobanian, H.; Frie, J.; Guo, Y.; Wu, Z.; Yu, Y.; Wang, M.		
Assignee Company:	Merck Sharp & Dohme Corp		
Disease Area:	Cardiovascular disease	**Biological Target:**	Renal outer medullary potassium (ROMK) channel (Kir1.l)

Summary: The regulation of ion flow across cellular membranes is a critical aspect of a wide range of biological processes. Nature has developed a broad array of ion channels capable of selectively transporting specific ions across membranes in response to a triggering event or signal. Voltage gated potassium channels, for example, open and close in response to changes in the voltage gradient across a cellular membrane. To date, 78 isoforms of voltage gated potassium channels have been identified. The majority are tetrameric, and the four transmembrane monomer subunits of these protein constructs contain six membrane spanning regions that form the walls of the channel. The inwardly rectifying potassium channel Kir1.1, also referred to as the renal outer medullary potassium channel (ROMK), is a member of this family of ion channels and plays a prominent role in kidney function. ROMK is part of the potassium recycling system across the luminal membrane that ensures proper function of the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending loop of Henle (TALH). In addition, ROMK has a significant impact on potassium secretion in the cortical collecting duct, which is tightly coupled to sodium uptake in this region. This channel has been the focus of significant research efforts, as it has been suggested that selective blockade of ROMK would produce diuretic activity that would have a positive impact on conditions such as hypertension and heart failure. It is also possible that ROMK blockade would lower blood pressure without causing hypokalemia, a potential side effect of conventional diuretics. The present application discloses a series of compounds that selectively block ROMK function and are potentially useful for the treatment of conditions in which diuretic activity would be beneficial.

Important Compound Classes:



Definitions:



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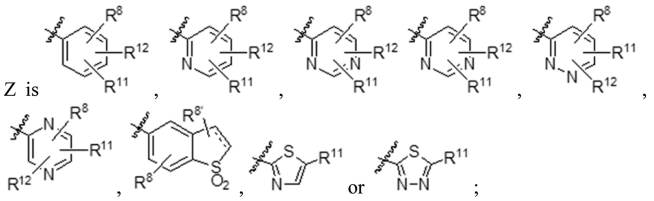
Y is -0- or a bond;

Z is 

Where ----- is a single or double bond;

R is independently H, alkyl, or halo alkyl;

R^1 is H, alkyl, −F, −OR, or $-N(R^{13})(R^{14})$;

R^2 is H or alkyl optionally substituted by 1−5 halogen atoms or −OR;

R^3 is H or alkyl;

R^4 is H or alkyl optionally substituted by 1−5 halogen atoms or −OR;

R^5 is H or alkyl optionally substituted by 1−5 halogen atoms or −OR;

or R^4 and R^5 are joined together to represent $-CH_2CH_2-$, $-CH_2NCH_2-$, $-CH_2N(CH_3)CH_2-$, or $-CH_2OCH_2-$;

R^6 is H, halo, alkyl optionally substituted by 1−5 halogen atoms or −OR, cycloalkyl, or −OR;

or R^6 and R^1 are joined together to represent $-CH_2CH_2O-$;

R^7 is H, halo, alkyl optionally substituted by 1−5 halogen atoms or −OR, cycloalkyl, or −OR;

R^8 is independently H or alkyl;

$R^{8'}$ is H or alkyl;

R^9 is −CN, tetrazolyl, or $-S(O)_2R^{13}$;

R^{10} is halo, −OR, alkyl optionally substituted by 1−5 halogen atoms or −OR, −S-alkyl, −N-alkyl, or −O-cyclopropyl;

R^{11} is −CN, $-S(O)_2R^{13}$, or optionally substituted heteroaryl (e.g., 1*H*-tetrazolyl, 2*H*-tetrazolyl, 1,2,4-oxadiazole, 4*H*-1,2,3-triazolyl or furanyl) wherein the optional substituent is halogen or alkyl;

R^{12} is H, halo, alkyl, cycloalkyl, or −OR;

R^{13} is H, alkyl, allyl, or cycloalkyl;

R^{14} is H, alkyl, or cycloalkyl;

R^{15} independently oxo, −F, −CN, alkyl optionally substituted by 1−5 fluorine atoms or −OR, cycloalkyl, heteroaryl optionally substituted by halogen, −CN, alkyl, or haloalkyl;

a is 1 or 2;

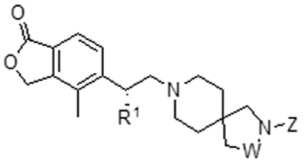
b is 0 or 1;

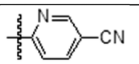
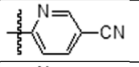
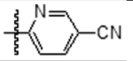
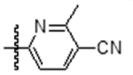
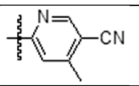
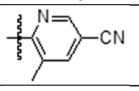
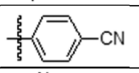
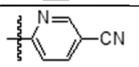
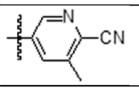
n is 0, 1, or 2;

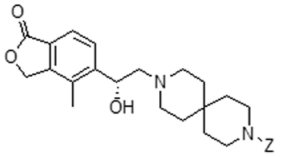
o is 1, 2, or 3; and

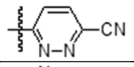
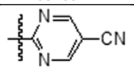
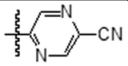
p is 1 or 2

Key Structures:



Example	R1	W	Z
1	OH	CO	
3	OH	CH_2	
4	H	CO	
9	OH	CH_2	
10	OH	CH_2	
11	OH	CH_2	
14	OH	CH_2	
79	NH_2	CO	
81	OH	CH_2	



Example	Z
105	
109	
111	

Recent Review Articles:

1. Garcia, M. L.; Kaczorowski, G. J. Targeting the inward-rectifier potassium channel ROMK in cardiovascular disease. *Curr. Opin. Pharmacol.* **2014**, *15*, 1−6.
2. Bhave, G.; Lonergan, D.; Chauder, B. A.; Denton, J. S. Small-molecule modulators of inward rectifier K+ channels: recent advances and future possibilities. *Future Med. Chem.* **2010**, *2* (5), 757−774.
3. Welling, P. A.; Ho, K. A. Comprehensive guide to the ROMK potassium channel: form and function in health and disease. *Am. J. Physiol.* **2009**, *297* (4), F849−F863.

Biological Assay: Thallium flux assay with HEK293 cells stably expressing hROMK (hKirl.l)

Biological Data:

Entry	IC_{50} (nM)	Entry	IC_{50} (nM)
1	10.5	14	15
3	10	79	14
4	12	81	10.1
9	14	109	14
10	17	111	9
11	20	105	13

Claims: 22 total claims
19 composition of matter claims
3 method claims

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Notes
The authors declare no competing financial interest.