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PATENT HIGHLIGHT

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Inhibitors of the Renal Outer Medullary Potassium Channel

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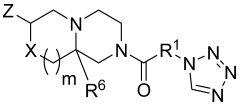
Title:	Inhibitors of the Renal Outer Medullary Potassium Channel		
Patent Application Number:	WO2013/028474A1	**Publication date:**	February 28th, 2013
Priority Application:	US 61/525,261	**Priority date:**	August 19th, 2011
	US 61/668.680		July 6th, 2012
Inventors:	Pasternak, A.; Blizzard, T.; Chobanian, H.; DeJesus, R.; Ding, F. X.; Dong, S.; Gude, C.; Kim, D.; Tang, H.; Walsh, S.; Pio, B.; Jiang, J.		
Assignee Company:	Merck, Sharp & Dohme Corp.		
Disease Area:	Cardiovascular Disease	**Biological Target:**	Kir1.1 (ROMK)

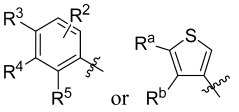
Summary: Voltage gated potassium channels play key roles in a variety of biological systems. To date, 78 isoforms have been identified. The inwardly rectifying potassium channel Kir1.1, also referred to as the renal outer medullary potassium channel, plays a prominent role in kidney function. In the thick ascending loop of Henle (TALH), the Kir1.1 channel is part of the potassium recycling system across the luminal membrane that ensures proper function of the $Na^+/K^+/2Cl^-$ cotransporter. Potassium secretion in the cortical collecting duct is also impacted by the presence of Kir1.1 in this region of the kidney and is tightly coupled to sodium uptake. It has been suggested that selective blockade of this channel would result in diuretic activity that would be useful for the treatment of conditions such as hypertension and heart failure. It has been further suggested that blockade of this channel 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 Kir1.1 function and are potentially useful for the treatment of conditions in which diuretic activity would be beneficial.

Important Compound Classes:

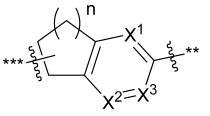


Definitions:

Z is



R^1 is



wherein *** indicates attachment to the carbonyl carbon and ** indicates attachment to the tetrazolyl ring;

X is O, NH, or S;

m is an integer selected from 1 or 2;

n is an integer selected from 1 or 2;

X^1, X^2, and X^3 are each independently selected from C(R^7) or N, provided that at least one of X^1, X^2, and X^3 must be N and at most two of X^1, X^2, and X^3 are N;

R^a is CN;

R^b is H or C_{1-6} alkyl;

R^2 is H, F, Cl, C_{1-6} alkyl, C_{3-6} cycloalkyl, or OC_{1-6}alkyl;

R^3 is H, F, Cl, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, or OC_{1-6}alkyl;

R^4 is F, Cl, CN, C_{3-6} cycloalkyl, OC_{1-4}alkyl, or *N*-tetrazolyl;

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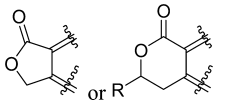
or R^3 and R^4 are joined together with the carbon atoms in the phenyl ring to which they are attached to form



wherein R is H or C_{1-4}alkyl;

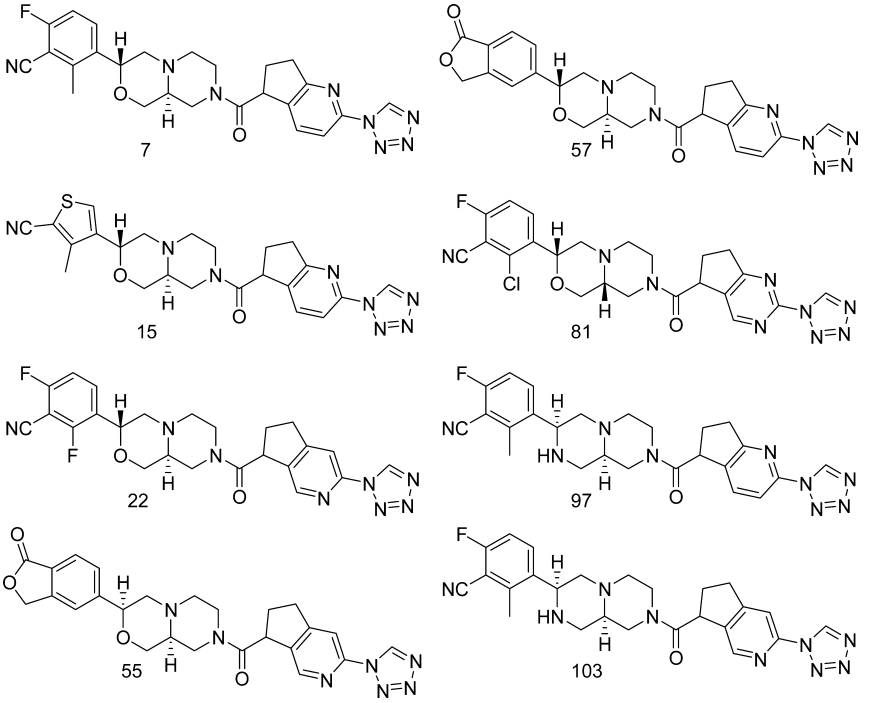
R^5 is H, Cl, F, CN, C_{1-4}alkyl, C_{3-6} cycloalkyl, or OC_{1-4}alkyl;

Provided that, when R^3 and R^4 are not joined together, one and only one of R^3, R^4, or R^5 is CN;

R^6 is H or C_{1-4}alkyl; and

R^7 is H, F, Cl, or C_{1-4}alkyl.

Key Structures:



Recent Review Articles:

1. 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.

2. Wang, W. H. Regulation of ROMK (Kir1.1) Channels: New Mechanisms and Aspects. *Am. J. Physiol. Renal Physiol.* **2006**, *290* (1), F14−F19.

Biological Assay:

K_{ir}1.1 Thallium flux assay, HEK293 cells stably expressing hK_{ir}1.1, FluxOR, FLIRP Tetra 384.

K_{ir}1.1 whole cell voltage clamp, CHO cells stably expressing hK_{ir}1.1, IonWorks Quattro.

Biological Data:

Entry	K_{ir}1.1 Th Flux (uM)	K_{ir}1.1Patch clamp (uM)	Entry	K_{ir}1.1Th Flux (uM)	K_{ir}1.1Patch clamp (uM)
7	0.14	0.08	57	0.11	0.09
15	0.54	0.06	81	0.17	0.06
22	0.16	0.04	97	0.16	0.09
55	0.14	0.06	103	0.18	0.10

Claims:

16 Total claims.

13 Composition of matter claims.

3 Method of use claims.

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Notes

The authors declare no competing financial interest.