



Universiteit
Leiden
The Netherlands

Allosteric modulation and ligand binding kinetics at the Kv11.1 channel

Yu, Z.

Citation

Yu, Z. (2015, October 20). *Allosteric modulation and ligand binding kinetics at the Kv11.1 channel*. Retrieved from <https://hdl.handle.net/1887/35951>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/35951>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/35951> holds various files of this Leiden University dissertation.

Author: Yu, Zhiyi

Title: Allosteric modulation and ligand binding kinetics at the Kv11.1 channel

Issue Date: 2015-10-20

Allosteric modulation and ligand binding kinetics

at the K_v11.1 channel

Zhiyi Yu

The research described in this thesis was performed in Division of Medicinal Chemistry at the Leiden Academic Centre for Drug Research, Leiden University (Leiden, The Netherlands).

Cover design: Shuo Mi and Zhiyi Yu

Thesis layout: Zhiyi Yu

Printed in the Netherlands

©Copyright, Zhiyi Yu, 2015. All right reserved.

No part of this book may be reproduced in any form or by any means without permission of the author.

Allosteric modulation and ligand binding kinetics at the $K_v11.1$ channel

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 20 oktober 2015
klokke 13:45 uur

door

Zhiyi Yu
geboren te Hubei, China
in 1986

Promotiecommissie

Promotor: Prof. Dr. A.P. IJzerman

Co-promotor: Dr. L.H. Heitman

Overige Leden: Prof. Dr. M. Danhof
Mevr. Prof. Dr. C. Mummery
Dr. M. van der Heyden
Prof. Dr. P.H. van der Graaf

Contents

Chapter 1	General introduction	7
Chapter 2	Kinetic studies of the $K_v11.1$ (hERG) channel	23
Chapter 3	Allosteric modulators of the $K_v11.1$ (hERG) channel: radioligand binding assays reveal allosteric characteristics of dofetilide analogues	63
Chapter 4	Allosteric modulation of $K_v11.1$ (hERG) channels protects against drug-induced ventricular arrhythmias	89
Chapter 5	Synthesis and biological evaluation of negative allosteric modulators of the $K_v11.1$ (hERG) channel	121
Chapter 6	$K_v11.1$ (hERG)-induced cardiotoxicity: a molecular insight from a binding kinetics study of prototypic $K_v11.1$ inhibitors	157
Chapter 7	Structure-affinity relationships (SARs) and structure-kinetics relationships (SKRs) of $K_v11.1$ (hERG) blockers	185
Chapter 8	Conclusions and perspectives	223
Summary		237
Samenvatting		241
Curriculum Vitae		245
List of publications		247
Acknowledgements		249

