

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: License 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

Curriculum Vitae

Zhiyi Yu was born on January 5th, 1986 in Hubei, China. After graduating from high school in 2004, he moved to Sichuan to study pharmacy in Western China School of Pharmacy at Sichuan University. In 2008 he received a bachelor degree, and then he continued a master study in the same university, majoring in medicinal chemistry. During this period he performed a series of studies on chemical synthesis and biological evaluation of antimicrobial compounds under the supervision of Prof. Taiping Hou.

After obtaining his master degree in 2011, Zhiyi Yu was supported by the China Scholarship Council to conduct a Ph.D study in Division of Medicinal Chemistry at the Leiden Academic Centre for Drug Research (Leiden University, The Netherlands) under the supervision of Prof. Ad IJzerman and Dr. Laura Heitman. His doctorate dissertation consisted of two main projects, which were allosteric modulation and ligand binding kinetics at the K_v11.1 (hERG) channel. During his Ph.D studies from 2011 to 2015, Zhiyi Yu together with his supervisors developed several valuable collaborations with Leiden University Medical Center and University Medical Center Utrecht, where he acquired different research skills in cellular electrophysiology. From October 2015 on, he will work as a postdoctoral fellow in the laboratory of Prof. Jonathan Cohen in Harvard Medical School at Harvard University. He will be applying protein chemistry as well as electrophysiological techniques to study allosteric modulations of neuronal AChRs and GABA_a receptors.

List of publications

- **Yu, Z.**; Liu, J.; van Veldhoven, J. P.; IJzerman, A. P.; Schalij, M. J.; Pijnappels, D. A.; Heitman, L. H.; de Vries, A. A. F. Allosteric Modulation of K_v11.1 (hERG) Channels Protects against Drug-Induced Ventricular Arrhythmias. *Circ. Arrhythm. Electrophysiol.* submitted.
- Yu, Z.; van Veldhoven, J. P.; Louvel, J. A.; 't Hart, I. M.; Kopf, A. H.; Heitman, L. H.; IJzerman, A. P. Synthesis and biological evaluation of negative allosteric modulators of the K_v11.1(hERG) channel. *Eur. J. Med. Chem.* submitted.
- **Yu, Z.**; van Veldhoven, J. P.; Louvel, J. A.; 't Hart, I. M.; Rook, M. B.; van der Heyden, M. A.; Heitman, L. H.; IJzerman, A. P. Structure-affinity relationships (SARs) and structure-kinetics relationships (SKRs) of K_v11.1 blockers. *J. Med. Chem.* **2015,** *58*, 5916-5929.
- **Yu, Z.**; IJzerman, A. P.; Heitman, L. H. K_v11.1 (hERG)-induced cardiotoxicity: a molecular insight from a binding kinetics study of prototypical K_v11.1 (hERG) inhibitors. *Br. J. Pharmacol.* **2015**, *172*, 940-955.
- Yu, Z.; Klaasse, E.; Heitman, L. H.; IJzerman, A. P. Allosteric modulators of the hERG K⁺ channel: Radioligand binding assays reveal allosteric characteristics of dofetilide analogs. *Toxicol. Appl. Pharmacol.* 2014, 274, 78-86.
- **Yu, Z.**; Shi, G.; Sun, Q.; Jin, H.; Teng, Y.; Tao, K.; Zhou, G.; Liu, W.; Wen, F.; Hou, T. Design, synthesis and *in vitro* antibacterial/antifungal evaluation of novel 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7(1-piperazinyl) quinoline-3-carboxylic acid derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 4726-4733.
- Vilums, M.; Zweemer, A. J.; Barmare, F.; van der Gracht, A. M.; Bleeker, D. C.; <u>Yu, Z.</u>; de Vries, H.; Gross, R.; Clemens, J.; Krenitsky, P.; Brussee, J.; Stamos, D.; Saunders, J.; Heitman, L. H.; IJzerman, A. P. When structure-affinity relationships meet structure-kinetics relationships: 3-((Inden-1-yl) amino)-1-iso-propyl-cyclopentane-1-carboxamides as CCR2 antagonists. *Eur. J. Med. Chem.* **2015,** *93*, 121-134.

- Vilums, M.; Zweemer, A. J.; <u>Yu, Z.</u>; de Vries, H.; Hillger, J. M.; Wapenaar, H.; Bollen, I. A.; Barmare, F.; Gross, R.; Clemens, J.; Krenitsky, P.; Brussee, J.; Stamos, D.; Saunders, J.; Heitman, L. H.; IJzerman, A. P. Structure-kinetic relationships-an overlooked parameter in hit-to-lead optimization: A case of cyclopentylamines as chemokine receptor 2 antagonists. *J. Med. Chem.* **2013**, *56*, 7706-7714.
- Louvel, J.; Carvalho, J. o. F.; \underline{Yu} , \underline{Z} ; Soethoudt, M.; Lenselink, E. B.; Klaasse, E.; Brussee, J.; IJzerman, A. P. Removal of human ether-à-go-go related gene (hERG) K⁺ channel affinity through rigidity: A case of clofilium analogues. *J. Med. Chem.* **2013**, *56*, 9427-9440.
- Carvalho, J. o. F.; Louvel, J.; Doornbos, M. L.; Klaasse, E.; <u>Yu, Z.</u>; Brussee, J.; IJzerman, A. P. Strategies to reduce hERG K⁺ channel blockade. Exploring heteroaromaticity and rigidity in novel pyridine analogues of dofetilide. *J. Med. Chem.* **2013**, *56*, 2828-2840.
- Wen, F.; Zhang, H.; <u>Yu, Z.</u>; Jin, H.; Yang, Q.; Hou, T. Design, synthesis and antifungal/insecticidal evaluation of novel nicotinamide derivatives. *Pestic. Biochem. Physiol.* **2010**, *98*, 248-253.
- Jin, H.; Geng, Y.; <u>Yu, Z.</u>; Tao, K.; Hou, T. Lead optimization and anti-plant pathogenic fungi activities of daphneolone analogues from Stellera chamaejasme L. *Pestic. Biochem. Physiol.* **2009**, *93*, 133-137.

Acknowledgements

The completion of this dissertation is one of the most significant challenges I have ever encountered. It is almost impossible to describe my acknowledgements to everyone who contributed to the realization of this dissertation. However, a large group of people should be mentioned within limited pages, as I could not have finished my Ph.D studies without their guidance, support and cooperation.

First and foremost, I would like to express my most sincere appreciation to my supervisors, Ad and Laura, for your continuous encouragement, insight and patience. I feel extremely privileged and fortunate to have been your student.

Secondly, I am deeply grateful to my collaborators, Marcel and Martin, Twan, Daniël, and in particular, Jia who is also my good friend.

Thirdly, a great debt of gratitude should be extended to my lovely colleagues and friends for all the wonderful times that we shared inside and outside of the laboratory. I feel very lucky, comfortable and relaxed to work in the Division of Medicinal Chemistry. I appreciated all people from this division for their help, kindness and support. Particularly, Elisabath and Dong trained me in different radioligand binding assays during my first semester. My officemates, Julien, Jaco, Maarten, Julia and Indira, provided a lot of assistance in both my professional and personal life. Other colleagues like Andrea, Arnault, Bart, Henk, Lance, Miriam, Natalia, Rongfang, Thea and Xue as well as my students (Erina, Renske, Rochelle, Tirsa and Wanisha) are also gratefully acknowledged. Likewise, there are a large group of friends, who I wish to thank for their help, outside of the medicinal chemistry division, such as Bingxiao, Changsheng, Cui, Dan, Debi, Emile, Hui, Jianbing, Kaixuan, Ke, Li, Lin, Qingju, Qiuhong, Shuo, Suyun, Xianqin, Yang, Yaowang, Yu, Yuejiao, and Zhengshan. In particular, Xianqin, Yang Wan and Zhengshan had given me a lot of help, advice and support since the first time I met them.

Last but not least, I am deeply indebted to my family members for all your unconditional and constant love, understanding, support and sacrifices during my studies. I particularly owe a great debt to my parents on whom I did not spend so much time. I had been far away from my parents since I went to the university in 2004. I should definitely accompany them more in the near future. Thanks very much for supporting and encouraging me spiritually throughout my life.