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Towards improved drug action : target binding kinetics and functional efficacy at the mGlu2 receptor

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Maarten L.J. Doornbos, Ilse Van der Linden, Liesbeth Vereyken, Gary Tresadern, Adriaan P. IJzerman, Hilde Lavreysen, Laura H. Heitman. *Constitutive activity of the metabotropic glutamate receptor 2 explored with a whole-cell label-free biosensor*. *Biochemical Pharmacology* 152 (2018) 201–210. doi:10.1016/j.bcp.2018.03.026.

Maarten L. J. Doornbos, Xuesong Wang, Sophie C. Vermond, Luc Peeters, Laura Pérez-Benito, Andrés A. Trabanco, Hilde Lavreysen, José María Cid, Laura H. Heitman, Gary Tresadern, Adriaan P. IJzerman. *A covalent allosteric probe for the metabotropic glutamate receptor 2: Design, synthesis and pharmacological characterization*. *Journal of Medicinal Chemistry*. Publication Date (Web) March 1, 2018. doi:10.1021/acs.jmedchem.8b00051.

Maarten L. J. Doornbos, José María Cid, Jordi Haubrich, Alexandro Nunes, Jasper W. van de Sande, Sophie C. Vermond, Thea Mulder-Krieger, Andrés A. Trabanco, Abdellah Ahnaou, Wilhelmus H. Drinkenburg, Hilde Lavreysen, Laura H. Heitman, Adriaan P. IJzerman, Gary Tresadern. *Discovery and Kinetic Profiling of 7-Aryl-1,2,4-triazolo[4,3-a]pyridines: Positive Allosteric Modulators of the Metabotropic Glutamate Receptor 2*. *Journal of Medicinal Chemistry* 60 (2017) 6704–6720. doi:10.1021/acs.jmedchem.7b00669.

Maarten L. J. Doornbos, Laura Pérez-Benito, Gary Tresadern, Thea Mulder-Krieger, Ilse Biesmans, Andrés A. Trabanco, José María Cid, Hilde Lavreysen, Adriaan P. IJzerman, Laura H. Heitman. *Molecular mechanism of positive allosteric modulation of the metabotropic glutamate receptor 2 by JNJ-46281222*. *British Journal of Pharmacology* 173 (2016) 588–600. doi:10.1111/bph.13390.

Not part of this thesis:

Maarten L.J. Doornbos and Laura H. Heitman. *Protocol for a Label-free impedance-based whole cell assay to study GPCR pharmacology*. Manuscript submitted; invitation from Methods in Cell Biology.

Laura Pérez-Benito, Maarten L.J. Doornbos, Arnau Cordoní, Luc Peeters, Hilde Lavreysen, Leonardo Pardo, Gary Tresadern. *Molecular Switches of Allosteric Modulation of the Metabotropic Glutamate 2 Receptor*. *Structure* 25 (2017) 1–10. doi: 10.1016/j.str.2017.05.021.

João F.S. Carvalho, Julien Louvel, Maarten L.J. Doornbos, Elisabeth Klaasse, Zhiyi Yu, Johannes Brussee, Adriaan P. IJzerman. *Strategies to reduce HERG K⁺ channel blockade. Exploring heteroaromaticity and rigidity in novel pyridine analogues of dofetilide*. *Journal of Medicinal Chemistry* 56 (2013) 2828–40. doi: 10.1021/jm301564f.

Annelien J.M. Zweemer, Indira Nederpelt, Hilde Vrieling, Sarah Hafith, Maarten L.J. Doornbos, Henk de Vries, Jeffrey Abt, Raymond Gross, Dean Stamos, John Saunders, Martine J. Smit, Adriaan P. IJzerman, Laura H. Heitman. *Multiple binding sites for small-molecule antagonists at the CC chemokine receptor 2*. *Molecular Pharmacology* 84 (2013) 551–61. doi: 10.1124/mol.113.086850.

CURRICULUM VITAE

Maarten Doornbos was born in Leiden on the 10th of May in 1989. After graduating from pre-university education at the Stedelijk Gymnasium Leiden in 2007 he started studying Bio-Pharmaceutical Sciences at Leiden University. The bachelor was finished with a research internship at the division of Medicinal Chemistry under supervision of Dr. Annelien Zweemer. The project focused on the molecular pharmacology of diverse ligands of the CC chemokine receptor 2 (CCR2). In September 2011 Maarten started the master Bio-Pharmaceutical Sciences. He performed a 9-month research internship at the division of Medicinal Chemistry which comprised two projects that were supervised by Dr. João Carvalho and Dr. Julien Louvel. The first project focused on the synthesis of novel molecules to gain molecular understanding of hERG channel blockade. The project resulted in a publication in the Journal of Medicinal Chemistry. The second project was focused on the synthesis of novel antagonists for the Adenosine A₁ receptor. From February 2013 onwards Maarten performed a 6-month research internship at the division of Neuroscience Discovery at Janssen Research and Development in Beerse, Belgium under supervision of Luc Peeters and Dr. Hilde Lavreysen. There he worked on a project focused on the mapping of the allosteric binding pocket of the metabotropic glutamate receptor 2 (mGlu₂) using a receptor-mutagenesis approach. The results obtained in this project are part of a publication in Structure.

After obtaining his master degree in September 2013 he started as a PhD candidate at the division of Medicinal Chemistry under supervision of Dr. Laura Heitman and Prof. Dr. Ad IJzerman. The project was a joined effort with the division of Neuroscience Discovery at Janssen Research and Development and was funded by the Vlaams Agentschap Innoveren & Ondernemen. Throughout his PhD studies Maarten presented parts of the work described in this thesis at several national and international conferences. He was invited speaker at various occasions, including the FIGON Dutch Medicines Days 2016 and 2017.

From May to September 2017 he worked as interim assistant professor in the division of Medicinal Chemistry. Currently, Maarten works as project manager at Catalyze in Amsterdam.



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