Acknowledgements

I would like to acknowledge the contribution of anyone who has contributed to the content of this thesis. Firstly, I would like to thank professor Meindert Danhof, professor Piet Hein van der Graaf and dr. Liesbeth de Lange for their conceptual preparation, innovative ideas and critical review of all elements in this work.

Secondly, I would like to thank my colleagues at the pharmacology department for the numerous critical discussions that provided new ideas and refined the results regarding the pharmacokinetic/pharmacodynamic and the modelling aspects of this work. This research was part of the IMI consortium Kinetics for Drug Discovery (K4DD), which enabled frequent discussions and exchange of expertise. I would like to thank professor Ad IJzerman and dr. Anke Mueller-Fahrnow for their leadership in this consortium and professor Steve Hill for leading the fellow program. I would like to thank all colleagues in the K4DD consortium for their helpful insights and critical discussions regarding the binding kinetics aspects in this thesis, especially Laura Heitman, Indira Nederpelt and Eric Wong. I am also grateful for the numerous discussions with professor Bert Peletier and dr. Vivi Rottschäffer about the mathematical aspects of my results.

Thirdly, I would like to thank my Master students Michelle Laerke, Joost Versfelt and Anna Vlot for their contribution to these results and their discussions with me to refine the results and their representation.

Finally, I would like to thank Janneke Klop for her critical support of my research and the visual and textual representation thereof.

Curriculum Vitae Wilbert de Witte

Wilbert de Witte started his studies in Bio-Pharmaceutical sciences at Leiden University in 2007. As part of the Master of Science programme, he performed internships in Organic Chemistry at the division of Bio-Organic synthesis and in pharmacokinetic/pharmacodynamic modeling at the division of Pharmacology, both at Leiden University. In 2013, he started his PhD research in the Pharmacology division of the Leiden Academic Centre for Drug Research under supervision of dr. Liesbeth de Lange, professor Piet van der Graaf and professor Meindert Danhof, which resulted in this thesis. His research aimed to identify the influence of drug-target binding kinetics on *in vivo* drug action by using modelling and simulation techniques. To identify this influence, drug-target binding kinetics are integrated with the other drivers of *in vivo* drug effects. This research was part of the IMI Kinetics for Drug Discovery (K4DD) consortium, which is a public-private partnership with several European universities and pharma companies. In October 2017, he started to work at Ablynx in Ghent as Modeling & Simulation scientist.

List of publications

Publications related to this thesis:

Witte, W.E.A. de, Danhof, M., Graaf, P.H. van der, and Lange, E.C.M. de (2017). The long residing negligence of target saturation **Nat. Rev. Drug Disc.** *Manuscript under revision*.

Witte, W.E.A. de, Vauquelin, G., Graaf, P.H. van der, and Lange, E.C.M. de (2017). The influence of drug distribution and drug-target binding on target occupancy: The rate-limiting step approximation. **Eur. J. Pharm. Sci.** *Epub ahead of print.*

Witte, W.E.A. de, Danhof, M., Graaf, P.H. van der, and Lange, E.C.M. de (2016). In vivo Target Residence Time and Kinetic Selectivity: The Association Rate Constant as Determinant. **Trends Pharmacol. Sci.** *37*: 831–842.

Witte, W.E.A. de, Wong, Y.C., Nederpelt, I., Heitman, L.H., Danhof, M., Graaf, P.H. van der, et al. (2015). Mechanistic models enable the rational use of in vitro drug-target binding kinetics for better drug effects in patients. **Expert Opin. Drug Discov**. *11*: 45–63.

De Lange, E.C.M., Van den Brink, W., Yamamoto, Y., de Witte, W.E.A., Wong, Y.C. (2017). Novel CNS drug discovery and development approach: model-based integration to predict neuro-pharmacokinetics and pharmacodynamics. **Expert Opin. Drug Discov**. *Epub ahead of print.*

Bot, I., Ortiz Zacarías, N. V., Witte, W.E.A. de, Vries, H. de, Santbrink, P.J. van, Velden, D. van der, et al. (2017). A novel CCR2 antagonist inhibits atherogenesis in apoE deficient mice by achieving high receptor occupancy. **Sci. Rep.** *7*: 52.

Schuetz, D.A., Witte, W.E.A. de, Wong, Y.C., Knasmueller, B., Richter, L., Kokh, D.B., et al. (2017). Kinetics for Drug Discovery: an industry-driven effort to target drug residence time. **Drug Discov. Today** *22*: 896–911.

Publications unrelated to this thesis:

Dubois, V.F.S., Witte, W.E.A. De, Visser, S.A.G., Danhof, M., and Pasqua, O. Della (2016). Assessment of Interspecies Differences in Drug-Induced QTc Interval Prolongation in Cynomolgus Monkeys, Dogs and Humans. **Pharm. Res.** *33*: 40–51.

Delft, P. Van, Witte, W. De, Meeuwenoord, N.J., Heden Van Noort, G.J. Van Der, Versluis, F., Olsthoorn, R.C.L., et al. (2014). Design of a ribosyltriazole-annulated cyclooctyne for oligonucleotide labeling by strain-promoted alkyne-azide cycloaddition. **European J. Org. Chem.** 2014: 7566–7571.

Walvoort, M.T.C., Witte, W. de, Dijk, J. van, Dinkelaar, J., Lodder, G., Overkleeft, H.S., et al. (2011). Mannopyranosyl uronic acid donor reactivity. **Org. Lett.** *13*: 4360–3.