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Development and application of novel scaffolds in drug discovery

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Appendix

Acknowledgements
List of Publications
About the Author



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André
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List of Publications

- **A. Boltjes**, A. Dömling, The Groebke-Blackburn-Bienaymé Reaction. *Eur. J. Org. Chem.* **2019**, (In Press, 10.1002/ejoc.201901124).
- **A. Boltjes**, H. X. Liu, H. P. Liu, A. Dömling, Ugi Multicomponent Reaction. *Org. Synth.* **2017**, *94*, 54-56.
- **A. Boltjes**, A. Shrinidhi, K. van de Kolk, E. Herdtweck, A. Dömling, Gd-TEMDO: Design, Synthesis, and MRI Application. *Chem-Eur J.* **2016**, *22*, 7352-7356.
- **A. Boltjes**, G. P. Liao, T. Zhao, E. Herdtweck, A. Dömling, Ugi 4-CR synthesis of gamma- and delta-lactams providing new access to diverse enzyme interactions, a PDB analysis. *Med. Chem. Comm.* **2014**, *5*, 949-952.
- **A. Boltjes**, Y. J. Huang, R. van de Velde, L. Rijke, S. Wolf, J. Gaugler, K. Lesniak, K. Guzik, T. A. Holak, A. Dömling, Fragment-Based Library Generation for the Discovery of a Peptidomimetic p53-Mdm4 Inhibitor. *Acs Comb. Sci.* **2014**, *16*, 393-396.
- S. Yerande, K. Newase, B. Singh, **A. Boltjes**, A. Dömling, Application of cyclic ketones in MCR: Ugi/amide coupling based synthesis of fused tetrazolo[1,5-a][1,4]benzodiazepines. *Med. Chem. Comm.* **2014**, *55*, 3263-3266.
- T. Zhao, **A. Boltjes**, E. Herdtweck, A. Dömling, Tritylamine as an Ammonia Surrogate in the Ugi Tetrazole Synthesis. *Org. Lett.* **2013**, *15*, 639-641.
- R. Wisastra, M. Ghizzoni, **A. Boltjes**, H. J. Haisma, F. J. Dekker, Anacardic acid derived salicylates are inhibitors or activators of lipoxygenases. *Bioorgan. Med. Chem.* **2012**, *20*, 5027-5032.
- M. Ghizzoni, **A. Boltjes**, C. de Graaf, H. J. Haisma, F. J. Dekker, Improved inhibition of the histone acetyltransferase PCAF by an anacardic acid derivative. *Bioorgan. Med. Chem.* **2010**, *18*, 5826-5834.

Conferences

- **A. Boltjes**, A. Dömling. *The Groebke-Blackburn-Bienaymé reaction: Two decades later*. Poster presentation: 7th International MCR 2018 Conference; 2018 Aug 26-31, Düsseldorf, Germany
- **A. Boltjes**, H. X. Liu, H. P. Liu, A. Dömling. *New approaches to employ the Ugi reaction, demonstrated through the synthesis of praziquantel*. Poster session presented: NWO CHAINS Conference; 2017 Dec 5-7, Veldhoven, The Netherlands
- **A. Boltjes**, A. Shrinidhi, K. van de Kolk, E. Herdtweck, A. Dömling. *The next generation of tetrazole based MRI Contrast Agents*. Orally presented at the MCB lecture series. 2014 Nov 27, Groningen, The Netherlands
- **A. Boltjes**, K. van de Kolk, E. Herdtweck, A. Dömling. *Development of a novel tetrazole based MRI contrast agent via the Ugi tetrazole reaction*. Orally presented at the annual congress; Figo Dutch Medicine Days; 2014 Oct 4-6; Ede, The Netherlands
- **A. Boltjes**, K. van de Kolk, E. Herdtweck, A. Dömling. *Gadolinium(III) based chelators by multi component reactions: a new class of potential MRI contrast agents*. Poster session presented: MCB2014 Conference; 2014 Aug 25-26, Groningen, The Netherlands
- **A. Boltjes**, G. P. Liao, T. Zhao, E. Herdtweck, A. Dömling. *Ugi 4-CR synthesis of gamma and delta lactams providing new acces to diverse enzyme interactions, a PDB analysis*. Poster session presented: MCB2014 Conference; 2014 Aug 25-26, Groningen, The Netherlands

About the Author

André Boltjes was born on the 10th of April 1984 in Wieringerwerf, The Netherlands. In 2007 he obtained his Bachelor degree in Organic and Analytical Chemistry at the Hanze University of Applied Sciences. For his graduation he worked on the development of new materials (hotmelts, coatings, foams, micro-encapsulation, etc.) in the field of polymer chemistry. After graduating, he started working at the University of Groningen as a technician for the Medicinal Chemistry group within the Groningen Research Institute of Pharmacy. In the initial years the focus was on the development of CNS drugs and prodrugs against conditions such as Parkinsons disease. Later, together with Prof. Frank Dekker, this focus moved to epigenetics and the synthesis of HAT and HDAC inhibitors. Finally, with the appointment of Prof. Alexander Dömling in 2011, his position developed into senior research technician/laboratory manager and was introduced to MCR chemistry. In 2014, under the supervision of Prof. Alexander Dömling, he proceeded with the basis of his doctorate work with attention to *Development and application of novel scaffolds in drug discovery*. The research resulted in multiple publications in peer reviewed journals which are described in this thesis.