SYNTHESIS OF 2,4-DIMETHYL-8-[2'-(2H-TETRAZOL-5-YL)-BIPHENYL-4-YLMETHYL]-5,8-DIHYDRO-6H-PYRIDO[2,3-D]PYRIMIDIN-7-ONE (TASOSARTAN) AND APPLICATION OF MICROWAVE ASSISTED ORGANIC SYNTHESIS

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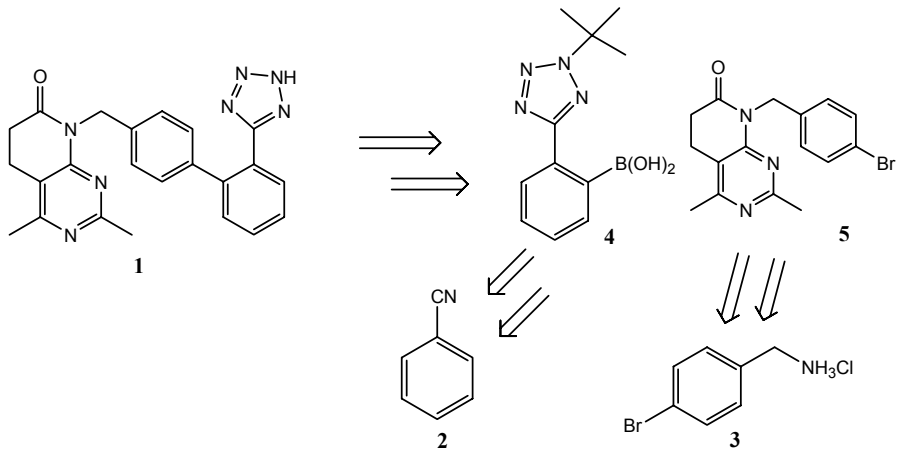
Introduction: The improved synthesis of 2,4-Dimethyl-8-[2'-(2H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-5,8-dihydro-6H-pyrido[2,3-d]pyrimidin-7-one (tasosartan) **1** on multigram-scale is described. Tasosartan is an angiotensin II antagonist for potential treatment of hypertension. Due to unresolved safety issues its NDA application was withdrawn in 1998. However, Tasosartan and its metabolites are still of interest in genomic and pharmaceutical studies [1]. Here the synthesis was developed in context of the DrugMatrix[2] genomics project.

Chemistry: 1 was synthesized according to literature known procedures [3,4] starting from 4-bromobenzylamine hydrochloride **2** and benzonitrile **3** in a convergent strategy, and the eight step synthesis was optimized using different reagents and applying microwave assisted organic synthesis (MAOS) [5] in several steps. The key step of the synthesis is the palladium catalysed coupling of boronic acid **4** with bromide **5**. For this reaction MAOS optimizations were first carried out on small scale, and then transferred to large scale MAOS using the newly developed Synthos 3000 from Anton Parr. The poster will disclose details of this optimization process.



Literature: [1] Jack D. *Drug News and perspectives,* **2000**, 13, 121-124. [2] http://www.iconicpharm.com/products/products_main.html. [3] Ellingboe J. W., Antane M., Nguyen T., Collini, M. D., Antane S., Bender R., Hartupee D., White V., McCallum J., *J. Med. Chem.*, **1994**, 37, 542-550. [4] Ellingboe J. W., Nikaido M., Bagli J. F., EP, 539086, **1993**. [5] For a recent review see: Kappe C.O., *Angew. Chem. Int. Ed.* **2004**, 43, 6250-6284.