ABSTRACT

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Title of diploma thesis: Effect of Synthetic Magnolol Derivatives on Activity of Nuclear Receptors PPARγ and RXRα

The nuclear receptors, peroxisome proliferator-activated receptor γ (PPARγ) and its heterodimerization partner retinoid X receptor α (RXRα) are drug targets in the treatment of diseases like the metabolic syndrome and *diabetes mellitus* type 2. The effort has been made to develop new agonists for PPARγ to obtain ligands with more favourable properties than currently used drugs (Berger et al. 2002, Berger et al. 2005).

Magnolol was previously described as a dual agonist of PPARγ and RXRα (Fakhrudin et al. 2010, Zhang et al. 2011). Based on the bi- aryl structure of magnolol, the effort has been made to design and synthesize linked magnolol dimers.

The aim of this thesis was to investigate the agonistic potential of these compounds with respect of the nuclear receptors PPARγ and RXRα in comparison to magnolol. We evaluated the ligand binding properties of the compounds and their functionality as PPARγ agonists *in vitro* and in intact cells, with a purified PPARγ ligand binding domain and in a cell-based nuclear receptor transactivation model in HEK293 cells, respectively.

We found that magnolol dimer binds with much higher affinity to the purified PPARγ ligand binding domain than magnolol (K_i values of 5.03 and 64.42 nM, respectively). However, there was no significant difference of PPARγ-dependent luciferase gene expression between magnolol dimer and between magnolol in intact cells. This is likely due to the PPARγ-specific activity of magnolol dimer, and the lack of RXRα activation by this compound (as specified above magnolol is dual PPARγ and RXRα agonist). The only derivative which is able to activate both receptors in intact cells is sesqui magnolol B, its affinity to PPARγ is similar to magnolol, but RXRα is affected only slightly.