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Synthesis and in vitro evaluation of magnolol based dimeric compounds as PPARγ agonists

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$PPAR_\gamma$ belongs to the superfamily of nuclear receptor proteins and upon activation by ligands acts as a transcription factor and regulates genes that are involved in glucose metabolism and lipid metabolism. Furthermore, activation of $PPAR_\gamma$ shows anti-inflammatory effects. Clinically used agonists (e.g. thiazolidinediones) are potent full agonists but exhibit serious side effects.

Partial agonism is hypothesized to reduce these side effects. Recently, three different neolignans (dieugenol, tetrahydrodieugenol and magnolol) were found to be $PPAR_\gamma$ partial agonists. Within this project we sought to optimize magnolol as a $PPAR_\gamma$ ligand. Preliminary molecular dockings studies and the crystal structure of $PPAR_\gamma$ with magnolol revealed that two molecules of magnolol bind to the active binding site of the receptor simultaneously.

The hypothesis was established that a molecule combining two magnolol structures would have increased affinity to the receptor and furthermore, it was hoped to have less side effects due to its expected partial agonism. In consequence, a dimeric compound (magnolol dimer) was designed by computational studies linking two magnolol molecules covalently via a spacer.

Here, we report the synthesis of the desired target molecule and three structurally simplified analogs (Figure 1). Subsequently, the synthesized compounds were evaluated towards their potential as $PPAR_\gamma$ agonists. Magnolol dimer showed an around 10 fold higher binding affinity towards a purified ligand binding domain than the parent compound magnolol. In a cellular luciferase reporter assay the dimeric compound and magnolol led to similar activation of $PPAR_\gamma$. As the receptor acts as a heterodimer with a second nuclear receptor, RXR, the two compounds were tested on RXR_α. While magnolol is able to activate RXR_α, the dimeric analog was completely inactive illustrating the great potential as a very selective activator.

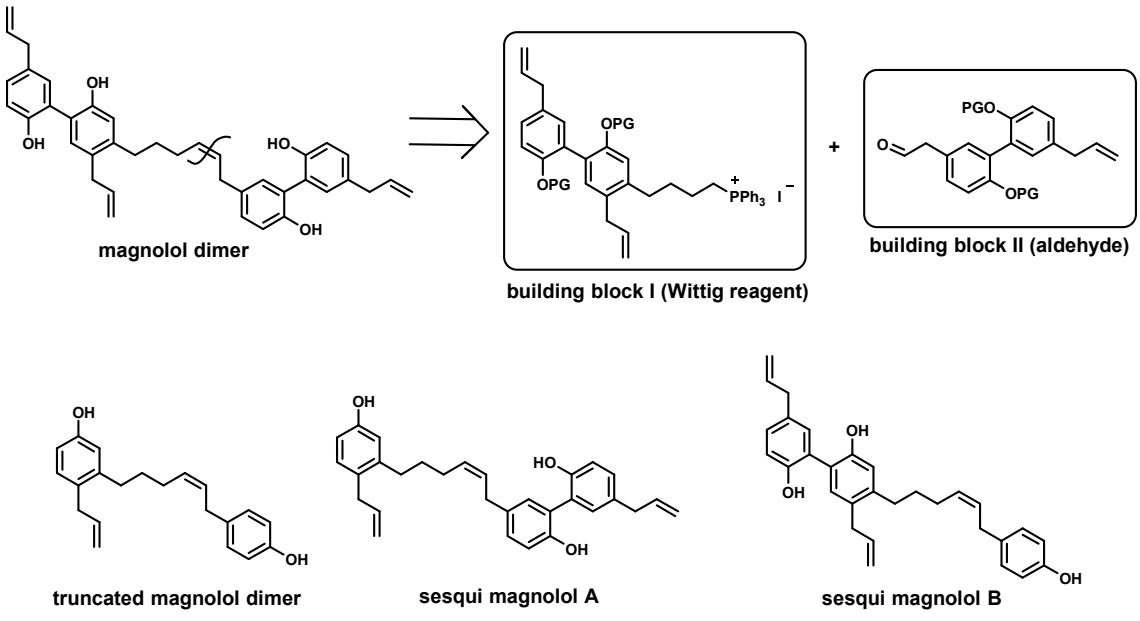

Figure 1: Magnolol dimer and structurally simplified compounds as pharmacological probes.

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