Short Lecture SL3

Synthesis of potential anti-inflammatory agents inspired by nature

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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. [1-2] Furthermore, activation of $PPAR_\gamma$ shows anti-inflammatory effects. [3] Clinically used agonists (thiazolidinediones) are potent full agonists but have serious side effects. Recently, three different neolignans (dieugenol, tetrahydrodieugenol and magnolol) were found to be $PPAR_\gamma$ partial agonists. [4] In the frame of this project it was sought to optimize magnolol as a $PPAR_\gamma$ ligand. Preliminary molecular dockings studies [4] and the crystal structure of PPARγ with magnolol [5] revealed that two copies of magnolol bind to the active binding site of the receptor simultaneously. The hypothesis was established that a molecule combining two magnolols 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 magnolol dimer was designed by computational studies linking two magnolol molecules covalently via a spacer. Here, we report the synthesis of a model compound featuring one and a half magnolol motifs (sesqui magnolol, Figure 1).

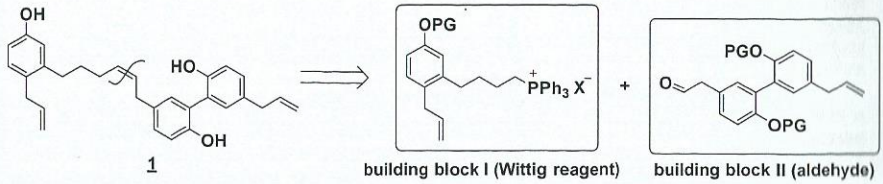

Figure 1: Sesqui magnolol 1 as a pharmaceutical probe and its synthesis.

For the synthesis of target compound 1 a classical Wittig reaction was envisioned as the crucial step to introduce the olefin in the required Z-configuration. Both building blocks were successfully synthesized starting from commercially available anisoles. Subsequent Wittig olefination gave the desired Z-isomer exclusively. Pharmacological probe 1 was obtained in good yields over 7 steps and its activity on $PPAR_\gamma$ was evaluated.

References:
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