P85

SYNTHESIS OF POTENTIAL ANTI-INFLAMMATORY AGENTS INSPIRED BY NATURE

Dreier D.[1], Rycek L.[1], Schuster D.[2], Atanasov A. G.[3], Dirsch V. M.[3], Schnürch M.[1], Mihovilovic M. D.[1]

[1] *Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-OC, A-1060 Vienna, Austria*

[2] *Institute of Pharmacy / Pharmaceutical Chemistry and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Innrain 80-82, A-6020 Innsbruck, Austria*

[3] *Departement of Pharmacognosy, University of Vienna, Althanstraße 14, A-1090 Vienna, Austria*

$PPAR_\gamma$ 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 (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. In the frame of this project it was sought to optimize magnolol as a $PPAR_\gamma$ ligand. Preliminary molecular dockings studies and the crystal structure of PPARγ with magnolol 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 the desired target molecule (Magnolol Dimer) and three structurally simplified analogs (Figure 1). Evaluation of the activity on $PPAR_\gamma$ is currently in progress.

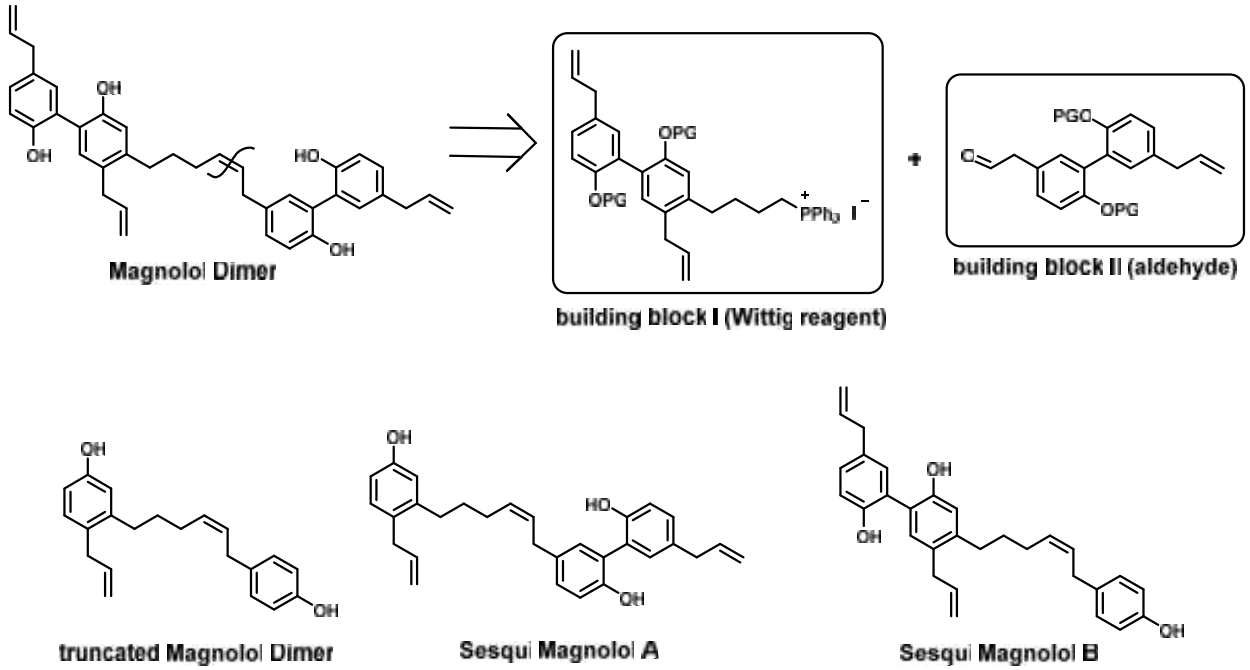

Figure 1: Magnolol Dimer and structurally simplified compounds as pharmacological probes.