Syntheses of Methotrexate-hybrid compounds for target profiling of small molecules with MASPIT

Dries De Clercq¹, Martijn Risseeuw¹, Sam Lievens², Jan Tavernier² and Serge Van Calenbergh¹

¹ Laboratory for Medicinal Chemistry (FFW), Ghent University, Harelbekestraat 72, B-9000 Gent, Belgium
² Cytokine Receptor Lab, Department of Medical Protein Research, VIB, Gent (Belgium) and Department of Biochemistry, Ghent University, Gent (Belgium)

To understand the molecular basis of the mode of action of organic small molecules, it is essential to identify their cellular target proteins. Mammalian small molecule-protein interaction trap (MASPIT[1]) provides a new tool for target-elucidation of small molecules, based on the cytokine-receptor-associated JAK-STAT-signal transduction system.

We set out to synthesize alkyne-functionalized analogues of blockbuster drugs (simvastatin, propranolol and tamoxifen) and the small molecule reversine, paying close attention to SAR. These analogues were conjugated with an azide containing MTX-reagent via the Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition (CLICK chemistry). The resulting MTX-conjugates are currently being evaluated in the MASPIT assay.