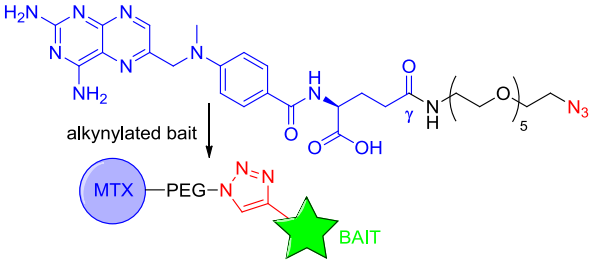
Syntheses of Methotrexate-hybrid compounds for target profiling of small molecules with MASPIT

Dries De Clercq[1], Martijn Risseeuw[1], Sam Lievens[2], Jan Tavernier[2] and Serge Van Calenbergh[1]

[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 Bio-chemistry, 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.

[1] Caligiuri, M.*et al. Chem. Biol.* **2006**, *13*, 711–722.