

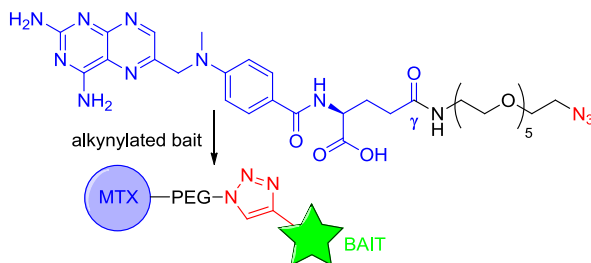
Syntheses of Methotrexate-hybrid compounds for target profiling of small molecules with MASPIT

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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.