

In situ Click Chemistry and Artificial Antibodies

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Click chemistry utilizes only the most practical and reliable chemical transformations. Among its applications in drug discovery, the target-templated in situ approach stands apart, for it allows the target itself to find its own best inhibitor through sampling multiple combinations of reactive building blocks.

The Huisgen 1,3-dipolar cycloaddition is particularly powerful in this context due to its high degree of dependability, complete specificity, and the bio-compatibility of the reactants. Moreover, the triazole linkage, likely due to its large dipole moment (ca. 5 Debye), is an aggressive pharmacophore, binding in strong and diverse ways to the proteins we have studied to date. High activation barrier of the reaction makes most azide and alkyne groups into demure reaction partners, and thence perfect for searching across the full range of chemical and biological systems, including states far from equilibrium, for just the right “molecular surroundings” to catalyze their concerted and permanent union into a new triazole linkage.