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Extended Abstract

Kinetic Target-Guided Synthesis as a Tool for Drug Discovery: Successes, Challenges, and Applications to Metalloproteases †

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Target-guided synthesis has emerged as an elegant and efficient lead- and drug-discovery strategy. Using the protein of interest as a vessel to catalyze the formation of its ligands is a rather novel concept, initially used by biochemists. It has gained a real interest in drug discovery in the past ten years.

In a kinetic target-guided synthesis (KTGS) [1], the biological target accelerates an irreversible reaction between a pair of reagents by stabilizing a productive configuration of the ternary complex. If the product is structurally similar to the transition state, its affinity for the protein is significantly improved compared to the affinity of reagents. The "click" chemistry is the most widely used KTGS reaction and was pioneered by Sharpless et al. [2].

After describing the history of the use of KTGS, the successes and challenges of this strategy from both a conceptual and practical point of view will be reviewed with case studies. An analysis of the chemical space of ligands discovered by KTGS will be presented. We will then present our work on the discovery of ligands, from compounds acting on transcriptional receptors to modulators of metalloproteases, among them the insulin degrading enzyme [3]. Finally, we will disclose some of our most recent work on metalloproteases of the M1 family.

References

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