Design and Synthesis of Conditionally Activatable Photolabile Protecting Groups

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Most chemotherapeutic agents are known to effectively inhibit the growth and division of cancerous cells, however, their insufficient selectivity results in severe side effects limiting their therapeutic use.[1] The use of light-activated drug release systems, by means of photolabile protecting groups (*photocages*) provides an opportunity to increase the selectivity through the spatiotemporally controlled release of biologically active agents.[2]

Our research group has recently conceptualized the bioorthogonally conditioned activatability of photolabile protecting groups (PPGs).[3] These conditionally photoactivatable photolabile protecting groups possess the characteristic of existing in a non-photoresponsive inactive form until they are activated in a bioorthogonal reaction. Following the bioorthogonal reaction, their photoresponsivity is restored and they become cleavable by light. While we have demonstrated the robustness of such conditionally activatable photocages in live cells through the spatiotemporally highly controlled liberation of a fluorogenic probe, these photocages are limited to blue-light activation due to the nature of the quenching mechanism exerted by an appending bioorthogonal motif, i.e., tetrazine. To address this limitation and to provide such PPGs with inherent targeting ability, we wished to extend conditional activation to enzymatic cleavage assisted arming of PPGs. We assumed that certain rhodol or xanthenium-based PPGs, recently developed in our group[4] can be rendered inactive upon modification of a key substituent on their frames. Removal of the disabling function leads to restoration of photoresponsivity.

We have designed conditionally activatable visible-light activatable PPGs that were modified with a self-immolative linker whose destruction can be triggered by means of enzymatic action. As a proof-of-principle we have explored the substrate of a model enzyme (porcine liver esterase) that can be easily overexpressed in cells. To be able to follow the process, a fluorogenic cargo was loaded onto the PPG (*Figure 1*).

Such conditionally photoactivatable systems can be extended to substrates of enzymes, whose overexpression is linked to certain cancers. We believe that the use of inherently targetable PPG-drug conjugates can be extended to phototherapeutic use as drug delivery systems.

[1] Xue, Y. et al. *Chem. Soc. Rev.* **2021**, *50*, 4872.
[2] Weinstain, R. et al. *Chem. Rev.* **2020**, *120*, 13135.
[3] Bojtár, M. et al. *J. Am. Chem. Soc.* **2020**, *142*, 15164.
[4] Egyed, A. et al. *J. Am. Chem. Soc.* **2023**, *145*, 4026.

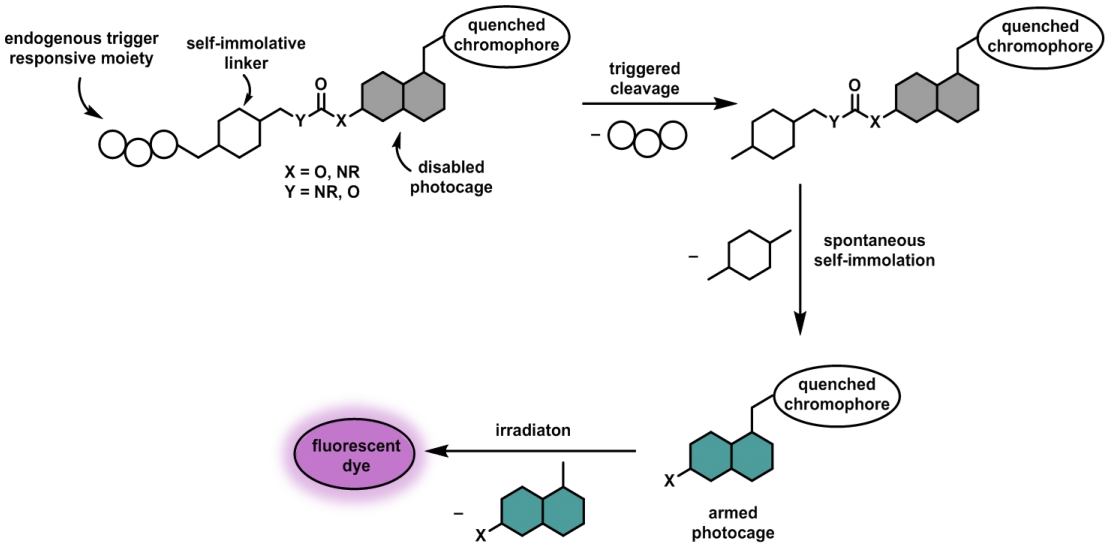

Figure 1: Schematic diagram of the conditional photoactivation