Amplification of Bioorthogonal 'Click-to-Release' Prodrugs for Targeted Anti-cancer Drug Delivery

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Abstract

Bioorthogonal self-immolative prodrug strategies should be selective and rapid to limit the off-target side effects common with traditional anti-cancer drug delivery approaches. Activation strategies that make use of the hydrolytic instability of 1,3-dipolar cycloaddition adducts following reaction of azides with trans-cyclooctene (TCO) provide exciting possibilities for the delivery of highly cytotoxic payloads.[1-3] However, release from an in vivo proof-of-concept prodrug displayed insufficient toxicity against a melanoma cell line, meaning further optimisation was required.[4]

A tetra-fluorinated electron deficient core, designed to facilitate a rapid click with TCO, was conjugated to a second, electron rich core, which allowed for independent control of click and release rates.[5] Modification of the releasing linkers indicated sustained and enhanced release from a 1,4/1,6-self immolating release core, which was linked via a N-methyl carbamate (Fig. 1). The second-order rate constant for cycloaddition with cis-dioxolane fused TCO (d-TCO) is, to the best of our knowledge, the fastest to date (22.0 M-1 s-1), an order of magnitude faster than with TCO and 4.5-fold faster than the previously reported rate. A persistent intermediate was observed, leading to sustained release of fluorophore from the branched scaffold, though activation under acidic conditions (pH 5.5) led to ≈ 15% higher fluorophore compared to activation at pH 7.4. The design allows for independent control of activation rates and drug release, allowing for a tuneable drug delivery system which could improve future pre-targeted in vivo bioorthogonal click-to-release prodrug strategies.

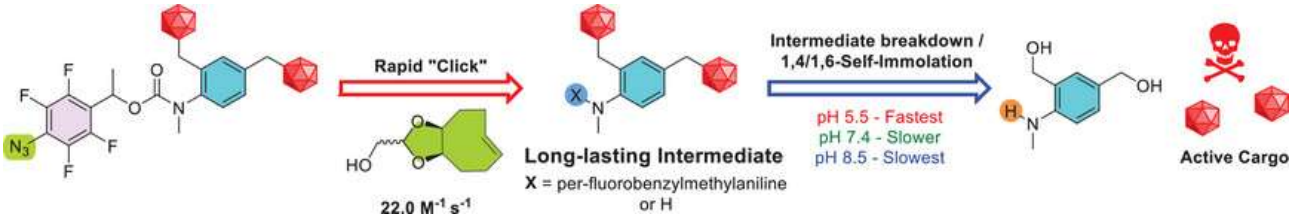

Figure 1. 'Dual-core' branched prodrug scaffold explored for tuneable release of cargo without compromising click reaction rate.

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Biography

Thomasin Brind is a medicinal chemist with expertise in biorthogonal drug delivery, linker design and small molecule synthesis. Following her undergraduate degree at the University of Southampton, she moved to Otago, where she worked on various projects with Associate Professor Bill Hawkins and Prof Nigel Lucas. She then began her PhD under the supervision of Assoc Prof Allan Gamble, focusing on click-to-release prodrugs. Her first postdoctoral position, with Gamble, investigated developing novel inhibitors for the treatment of tuberculosis. She is now preparing to start her second postdoc position at the University of Sydney with Assoc Prof Yu Heng Lau.